

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07D 413/06, 401/06, 417/06 C07D 405/06, 409/06, 403/06 A61K 31/41, 31/445</p>	A1	<p>(11) International Publication Number: WO 93/21181</p> <p>(43) International Publication Date: 28 October 1993 (28.10.93)</p>												
<p>(21) International Application Number: PCT/GB93/00788</p> <p>(22) International Filing Date: 14 April 1993 (14.04.93)</p> <p>(30) Priority data:</p> <table border="0"> <tr> <td>9208323.7</td> <td>15 April 1992 (15.04.92)</td> <td>GB</td> </tr> <tr> <td>9216065.4</td> <td>28 July 1992 (28.07.92)</td> <td>GB</td> </tr> <tr> <td>9219686.4</td> <td>17 September 1992 (17.09.92)</td> <td>GB</td> </tr> <tr> <td>9226069.4</td> <td>14 December 1992 (14.12.92)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BAKER, Raymond [GB/GB]; Bulls Cottage, Green Tye, Much Hadham, Hertfordshire SG10 6JN (GB). LADDHWAHETTY, Tamara [GB/GB]; 185 Buckhurst Way, Buckhurst Hill, Essex IG9 6JB (GB). SEWARD, Eileen Mary [IE/GB]; 15 The Colts, Thorley Park, Bishops Stortford, Hertfordshire CM23 4DL (GB). SWAIN, Christopher, John [GB/GB]; 8 Mangers Lane, Duxford, Cambridge CB2 4RN (GB).</p>		9208323.7	15 April 1992 (15.04.92)	GB	9216065.4	28 July 1992 (28.07.92)	GB	9219686.4	17 September 1992 (17.09.92)	GB	9226069.4	14 December 1992 (14.12.92)	GB	<p>(74) Agent: QUILLIN, Helen, Kaye; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
9208323.7	15 April 1992 (15.04.92)	GB												
9216065.4	28 July 1992 (28.07.92)	GB												
9219686.4	17 September 1992 (17.09.92)	GB												
9226069.4	14 December 1992 (14.12.92)	GB												
<p>(54) Title: AZACYCLIC COMPOUNDS</p> <div style="text-align: center; margin: 20px 0;"> </div> <p style="text-align: right; margin-right: 50px;">(I)</p> <p>(57) Abstract</p> <p>Compounds of formula (I), and salts and prodrugs thereof wherein n is 1, 2 or 3; X represents O or S; Y represents a hydrocarbon chain of 1, 2, 3 or 4 carbon atoms optionally substituted by oxo; R¹ is phenyl optionally substituted by 1, 2 or 3 of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b; R² is phenyl, indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl, quinolyl, benzhydryl, or benzyl; R⁴ and R⁵ each independently represent H, halo, C₁₋₆alkyl, oxo, CH₂OR^a, CO₂R^a or CONR^aR^b; R⁸ represents an optionally substituted aromatic heterocycle; and R^a and R^b are H, trifluoromethyl, C₁₋₆alkyl or phenyl optionally substituted by C₁₋₆alkyl, halo or trifluoromethyl; are tachykinin antagonists useful in medicine.</p>														

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

- 1 -

AZACYCLIC COMPOUNDS

5 This invention relates to a class of azacyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azacyclic ring system substituted by an arylmethoxy or arylmethylthio moiety.

10 The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

15 Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

20 Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, J. Med Chem, (1982) 25 1009; S.L. Shephard et al, Br. J. Pharmacol. (1993), 108, 11-12) and in arthritis [Levine et al in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI

- 2 -

tract such as inflammatory bowel disease [Mantyh et al in Neuroscience (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is

5 also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid

10 Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other

15 disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9]

20 vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner et al Science, (1990) 250, 279-82] in senile dementia of the Alzheimer type,

25 Alzheimer's disease and Down's Syndrome.

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod et. al., poster presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992], and in disorders of bladder function

30 such as bladder detrusor hyper-reflexia (Lancet, 16th May, 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders:

- 3 -

depression, dysthymic disorders, chronic obstructive
airways disease, hypersensitivity disorders such as
poison ivy, vasospastic diseases such as angina and
Reynauld's disease, fibrosing and collagen diseases such
5 as scleroderma and eosinophillic fascioliasis, reflex
sympathetic dystrophy such as shoulder/hand syndrome,
addiction disorders such as alcoholism, stress related
somatic disorders, neuropathy, neuralgia, disorders
related to immune enhancement or suppression such as
10 systemic lupus erythmatosis (European patent application
no. 0 436 334), ophthalmic disease such as conjunctivitis,
vernal conjunctivitis, and the like, and cutaneous
diseases such as contact dermatitis, atropic dermatitis,
urticaria, and other eczematoid dermatitis (European
15 patent application no. 0 394 989) and emesis (European
patent application no. 0 533 280).

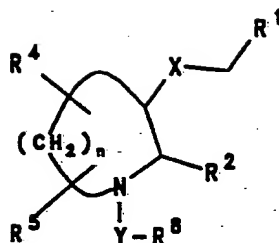
In view of their metabolic instability, peptide
derivatives are likely to be of limited utility as
therapeutic agents. It is for this reason that non-
20 peptide tachykinin antagonists are sought.

European patent application no. 0 436 334
discloses 4- to 7-membered azacyclic compounds
substituted at the 3-position by a substituted amino
moiety. The compounds are said to be tachykinin
25 antagonists.

The present invention provides a compound of
formula (I), or a salt or prodrug thereof:

30

- 4 -



(I)

10 wherein

n is 1, 2 or 3;

X represents O or S;

Y represents a hydrocarbon chain of 1, 2, 3 or
 15 4 carbon atoms which may optionally be substituted by
 oxo;

R¹ represents phenyl optionally substituted by
 1, 2 or 3 groups selected from C₁-6alkyl, C₂-6 alkenyl,
 C₂-6alkynyl, halo, cyano, nitro, trifluoromethyl,
 trimethylsilyl, -OR^a, SR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b,
 20 -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b;

R² represents aryl selected from phenyl and
 naphthyl; heteroaryl selected from indazolyl, thienyl,
 furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl;
 benzhydryl; or benzyl; wherein each aryl or heteroaryl
 25 moiety may be substituted by C₁-6alkyl, C₁-6alkoxy, halo
 or trifluoromethyl;

R⁴ and R⁵ may be present on any available
 carbon atom of the azacyclic ring and each independently
 represent H, halo, C₁-6alkyl, oxo, CH₂OR^a, CO₂R^a or
 30 CONR^aR^b;

R⁸ represents an optionally substituted
 aromatic heterocycle; and

- 5 -

R^a and R^b each independently represent H, trifluoromethyl, C_{1-6} alkyl or phenyl optionally substituted by C_{1-6} alkyl, halo or trifluoromethyl.

As used herein, the definition of each
5 expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred
to with respect to the above formula may represent
10 straight, branched or cyclic groups, or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as
15 cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

The present invention includes within its scope
20 prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and
25 preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. In
30 particular, the relative orientation of the 2- and 3-substituents on the azacyclic ring may give rise to cis and trans diastereoisomers, of which the cis stereochemistry is preferred. It is to be understood

- 6 -

that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

Preferably n is 2 or 3, more preferably 3.

Preferably X represents O .

5 Suitably Y represents a hydrocarbon chain of 1 or 2 carbon atoms optionally substituted by oxo, such as CH_2 , $C=O$, $CH(CH_3)$, $CH_2(C=O)$ or $(C=O)CH_2$. Preferably Y represents CH_2 , $CH(CH_3)$ or $CH_2(C=O)$, more preferably CH_2 or $CH(CH_3)$. A particularly preferred subgroup of
10 compounds according to the invention is represented by compounds of formula (I) wherein Y is $CH(CH_3)$.

 Preferably R^1 represents substituted phenyl. When R^1 is substituted phenyl suitable substituents include nitro, trifluoromethyl, trimethylsilyl, bromo,
15 chloro, fluoro, iodo, cyano, C_{1-6} alkyl such as methyl, ethyl, *i*-propyl, *i*-butyl, *t*-butyl and cyclopropyl, C_{2-6} alkenyl such as vinyl, C_{1-6} alkoxy such as methoxy, ethoxy and *i*-propoxy, phenoxy, amino, carboxamido and carbonylmethoxy. Preferably R^1 represents phenyl
20 substituted by one or more groups selected from C_{1-4} alkyl, such as methyl and *t*-butyl, trifluoromethyl and halo such as iodo, bromo chloro and fluoro.

 Suitably R^1 represents monosubstituted phenyl, such as 3-substituted phenyl or, preferably,
25 disubstituted phenyl, such as 3,5-disubstituted phenyl. Preferably R^1 represents phenyl substituted at the 3-position by trifluoromethyl or a C_{1-6} alkyl group such as *t*-butyl, or 3,5-disubstituted phenyl wherein the substituents are independently selected from
30 trifluoromethyl, chloro, fluoro, methyl and *t*-butyl. Preferred values for R^1 include 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-*t*-butyl-5-methylphenyl, 3-chloro-5-methylphenyl, 3-*t*-butyl-5-chlorophenyl, 3-bis(trifluoromethyl)phenyl and 3-*t*-

- 7 -

butylphenyl. Particularly preferred is 3,5-bis(trifluoromethyl)phenyl.

Suitably R^2 represents benzhydryl or optionally substituted phenyl, such as phenyl optionally substituted
5 by halo such as fluoro or chloro, preferably in the 3-position. Preferably R^2 represents unsubstituted phenyl or unsubstituted benzhydryl, more preferably unsubstituted phenyl.

Suitable values for R^4 and R^5 include H,
10 C_{1-6} alkyl, especially methyl, hydroxymethyl and oxo. The substituents R^4 and R^5 may be located on any available carbon atom of the azacyclic ring including, except in the case where the substituent R^4 or R^5 in question represents oxo, C-2 and C-3. Preferably at least one of
15 R^4 and R^5 represents H. In one preferred group of compounds R^4 and R^5 both represent H. In a further preferred group of compounds one of R^4 and R^5 is H and the other of R^4 and R^5 is methyl, preferably 2-methyl.

When R^8 represents a substituted aromatic
20 heterocycle, suitable substituents in the heterocyclic ring include one or more of C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, oxo, thioxo, halo, trifluoromethyl, NR^aR^b , NR^aCOR^b , $CONR^aR^b$, CO_2R^a , SR^a , SO_2R^a and CH_2OR^a , where R^a and R^b are as previously defined. Particular examples of
25 suitable substituents include methyl, methoxy, phenyl, oxo, thioxo, bromo, iodo, NH_2 , SCH_3 , $CONH_2$ and cyano. Particularly preferred substituents include oxo and NH_2 .

Suitable values for R^8 include thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl,
30 thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl,

- 8 -

benzofuranyl and indolyl, any of which may be substituted.

In particular, R⁸ may represent optionally substituted thienyl, furyl, pyridyl, triazolyl, 5 tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, benzimidazolyl or benzoxazolyl.

In one group of compounds according to the invention R⁸ represents optionally substituted pyrrolyl, 10 pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl or indolyl.

Preferably R⁸ represents a substituted or 15 unsubstituted 5- or 6-membered nitrogen containing aromatic heterocycle such as for example oxazolyl, oxadiazolyl, tetrazolyl, thiazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridazinyl, imidazolyl or triazinyl. More preferably R⁸ represents 20 optionally substituted oxazolyl, oxadiazolyl, imidazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl or triazinyl, or tetrazolyl substituted by C₁₋₆alkyl, preferably methyl.

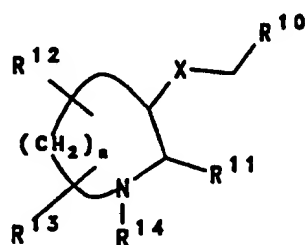
In one preferred group of compounds according 25 to the invention, R⁸ represents substituted or unsubstituted oxadiazolyl, for example, oxadiazolyl substituted by halo, amino, dialkylamino or methyl. More preferably R⁸ represents 5-(3-aminooxadiazolyl).

In a further preferred group of compounds 30 according to the invention, R⁸ represents substituted or unsubstituted triazolyl, for example, unsubstituted triazolyl or triazolyl substituted by oxo or thioxo, more preferably, triazolyl substituted by oxo.

- 9 -

It will be appreciated that, when the heterocyclic moiety R^8 is substituted by an oxo or thioxo substituent, different tautomeric forms are possible so that the substituent may be represented as =O or -OH, or
 5 =S or -SH, respectively. For the avoidance of doubt, all such tautomeric forms are embraced by the present invention.

One subgroup of compounds according to the invention is represented by compounds of formula (IA),
 10 and salts and prodrugs thereof:



(IA)

20 wherein

n is 1, 2 or 3 and where any carbon atom of $(CH_2)_n$ may be substituted by R^{12} and/or R^{13} ;

X represents O or S;

R^{10} represents phenyl optionally substituted by
 25 1, 2 or 3 groups selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^C$, SR^C , SOR^C , SO_2R^C , $-NR^C R^d$, $-NR^C COR^d$, $-NR^C CO_2R^d$, $-CO_2R^C$ or $-CONR^C R^d$;

R^{11} represents aryl selected from phenyl and
 30 naphthyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each aryl or heteroaryl moiety may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl;

- 10 -

R^{12} and R^{13} each independently represent H, halo, C_{1-6} alkyl, oxo, CO_2R^C or $CONR^C R^d$;

R^{14} represents C_{1-4} alkyl, optionally substituted by oxo, substituted by an optionally substituted aromatic heterocycle; and

R^C and R^d each independently represent H, C_{1-6} alkyl, phenyl optionally substituted by C_{1-6} alkyl or halo or trifluoromethyl.

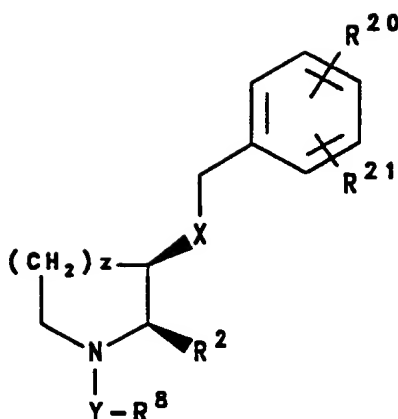
Suitable values for the heterocyclic moiety of R^{14} include thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyridazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl and indolyl.

In one sub-class of compounds of formula (IA), R^C and R^d each independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl.

A further subclass of compounds of formula (IA) is represented by compounds wherein n is 2 or 3; R^{12} and R^{13} each independently represent H, halo, C_{1-6} alkyl, CO_2R^C or $CONR^C R^d$; R^{14} represents C_{1-4} alkyl substituted by an optionally substituted 5- or 6-membered aromatic heterocycle; and R^C and R^d each independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl. For the compounds of this subclass, suitable values for the heterocyclic moiety of R^{14} include thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl and imidazolyl.

A preferred sub-class of compounds according to the invention is represented by compounds of formula (IB), and salts and prodrugs thereof:

- 11 -



(IB)

wherein

- 15 X represents O or S, preferably O;
 Y is as defined for formula (I), preferably
 C₁-2alkyl optionally substituted by oxo, more preferably
 CH₂ or CH(CH₃);
 R² represents phenyl or benzhydryl wherein any
 20 of the phenyl rings of the phenyl or benzhydryl moieties
 may optionally be substituted by halo or trifluoromethyl,
 preferably unsubstituted phenyl;
 R⁸ is as defined for formula (I); and
 R²⁰ and R²¹ independently represent H,
 25 C₁-6alkyl, C₂-6alkenyl, C₂-6alkynyl, bromo, chloro,
 fluoro, iodo, cyano, nitro, trifluoromethyl,
 trimethylsilyl, OR^a, SR^a, SOR^a, SO₂R^a, NR^aR^b, NR^aCOR^b,
 NR^aCO₂R^b, COR^a, CO₂R^a or CONR^aR^b, where R^a and R^b are as
 previously defined; and
 30 z is 1 or 2.
 Particular values of R²⁰ and R²¹ include H,
 methyl, t-butyl, methoxy, i-propoxy, chloro, fluoro,
 nitro, amino, carbonylmethoxy, carboxamido and
 trifluoromethyl. Preferably R²⁰ and R²¹ are both other

- 12 -

than H, more preferably C₁₋₆alkyl, halo or trifluoromethyl, and are located at the 3- and 5-positions of the phenyl ring.

One sub-class of compounds according to the invention are compounds of formula (IB) wherein R⁸ is optionally substituted pyrrolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl, indolyl, thiadiazolyl or oxadiazolyl, more preferably oxadiazolyl.

A further sub-class of compounds according to the invention are compounds of formula (IB) wherein R⁸ is optionally substituted oxadiazolyl, pyridinyl, benzimidazolyl, tetrazolyl, thiazolyl, furyl, thienyl, triazolyl, thiadiazolyl, benzoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, triazinyl, pyrimidinyl or imidazolyl.

A particularly preferred group of compounds according to the invention are compounds of formula (Ia) wherein R⁸ is optionally substituted triazolyl, especially triazole substituted by oxo.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention (such as the dibenzoyltartrate salts) or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, oxalic acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic

- 13 -

acid, phosphoric acid or p-toluenesulphonic acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

Preferred salts of the compounds according to the invention include the hydrochloride and p-toluenesulphonic acid salts.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose,

- 14 -

sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils

- 15 -

such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums
5 such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically
10 acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route
15 for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or
20 intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The compounds of formula (I) are of value in
25 the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia;
30 neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other

- 16 -

neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intracranial pressure; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. For example, the compounds of

- 17 -

formula (I) may suitably be used in the treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type,
5 Alzheimer's disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as
10 inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as
15 ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine.

20 The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other
25 neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

- The present invention further provides a compound of formula (I) for use in therapy.

30 According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

- 18 -

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises
5 administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the
10 present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor
15 antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The present invention accordingly provides a
20 method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

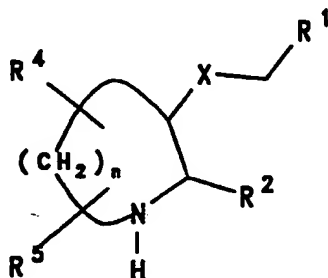
25 The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated
30 with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg of a compound of formula (I) per day. For example, in the treatment of conditions involving the

- 19 -

neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

According to one general process (A), the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula (II):



(II)

wherein R^1 , R^2 , R^4 , R^5 , X and n are as defined for formula (I) above, with a reagent suitable to introduce the group $Y-R^8$, for example, a halide or acyl halide, or corresponding mesylate or tosylate, of formula R^8-Y-L , where L represents halo, such as chloro, bromo or iodo, methylsulphonate or *p*-toluenesulphonate, or any other suitable leaving group, in the presence of a base.

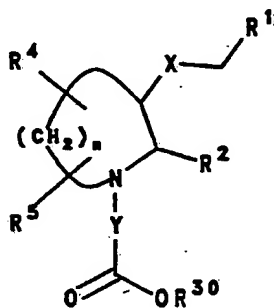
Suitable bases of use in the reaction include inorganic bases such as alkali metal carbonates, for example, potassium carbonate.

Conveniently the reaction is effected in a suitable organic solvent, for example, dimethylformamide.

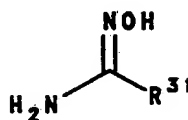
According to a second process (B), compounds of formula (I) wherein R^8 represents 5-oxadiazolyl may be

- 20 -

prepared by reaction of a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I), R^{30} represents an alkyl group and R^{31} represents H or a suitable substituent such as C_{1-6} alkyl, C_{1-6} alkoxy, halo, NR^aR^b or NR^aCOR^b , where R^a and R^b are as previously defined, in the presence of a base.

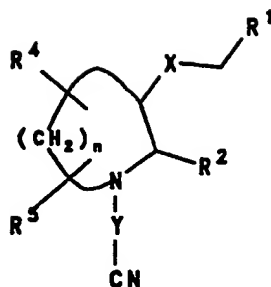
Suitable bases of use in the reaction include alkali metals, such as, for example, sodium, and alkali metal hydrides, such as, for example, sodium hydride.

The reaction is conveniently effected in a suitable organic solvent. Which solvents will be appropriate will depend on the nature of the base used. For example, where the base used is an alkali metal, suitable solvents will include alcohols, for example, ethanol, whereas where the base used is an alkali hydride, suitable solvents will include ethers, for example, tetrahydrofuran.

Preferably the reaction is conducted at elevated temperature, such as the reflux temperature of the chosen solvent.

According to a further process, (C), compounds of formula (I) wherein R^8 represents tetrazolyl may be prepared from intermediates of formula (V):

- 21 -

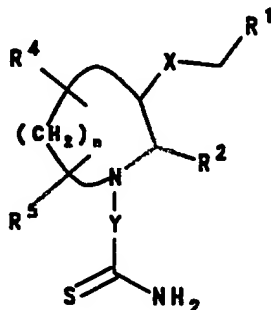


(V)

wherein R^1 , R^2 , R^4 , R^5 , X, Y and n are as defined for formula (I) by treatment with an alkali metal azide, such as sodium azide.

The reaction is conveniently effected in a high boiling organic solvent, such as, for example, N-methylpyrrolidinone.

According to a further process, (D), compounds of formula (I) wherein R^8 represents thiazolyl may be prepared from intermediates of formula (VI):



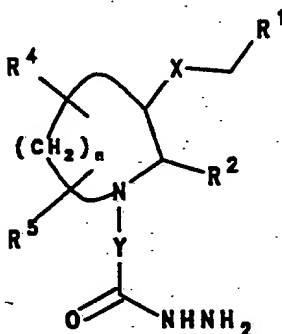
(VI)

wherein R^1 , R^2 , R^4 , R^5 , X, Y and n are as defined for formula (I), by reaction with a compound of formula $\text{Hal-CH}_2\text{C(O)-R}^{60}$, where Hal represents halo, such as bromo, chloro or iodo, and R^{60} represents H or a suitable substituent such as C_{1-6} alkyl.

- 22 -

The reaction is conveniently effected in a suitable organic solvent, such as a ketone, for example, acetone, or an alcohol, for example, methanol, or a mixture of solvents, preferably at elevated temperature, such as the reflux temperature of the chosen solvent.

According to a further process, (E), compounds of formula (I) wherein R^8 represents thioxotriazolyl may be prepared from intermediates of formula (VII)



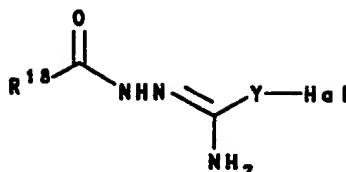
(VII)

wherein R^1 , R^2 , R^4 , R^5 , X, Y and n are as defined for formula (I), by reaction with a compound of formula $R^{61}NCS$, wherein R^{61} represents H or a suitable substituent such as C_{1-6} alkyl, in the presence of a base.

Suitable bases of use in the reaction include organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is conveniently effected in a suitable organic solvent, such as alcohol, e.g. butanol.

According to a further process, (F), compounds of formula (I) wherein R^8 represents unsubstituted or substituted triazolyl may be prepared by reaction of intermediates of formula (II) with a compound of formula (VIII):

- 23 -



(VIII)

wherein Y and Hal are as previously defined and R¹⁸ is H
or a group suitable as a substituent of the triazole
ring, or convertible to such a group under the reaction
conditions, in the presence of a base.

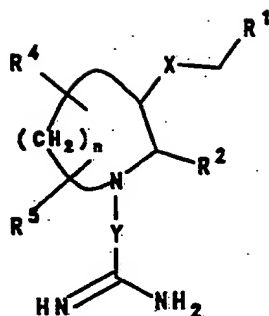
Suitable bases of use in the reaction include
alkali metal carbonates, such as, for example, potassium
carbonate.

Suitably R¹⁸ represents H, OCH₃ (which is
converted to an oxo substituent under the reaction
conditions) or CONH₂.

The reaction is conveniently effected in an
anhydrous organic solvent, such as, for example,
anhydrous dimethylformamide, preferably at elevated
temperature, such as about 140°C.

According to a further process, (G), compounds
of formula (I) wherein R⁸ represents substituted or
unsubstituted 1,3,5-triazine may be prepared by reaction
of intermediates of formula (IX):

- 24 -

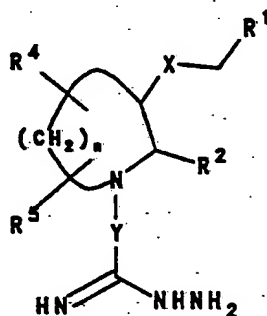


(IX)

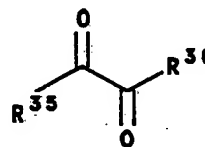
wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I), with substituted or unsubstituted 1,3,5-triazine.

15 The reaction is conveniently effected in a suitable organic solvent, such as acetonitrile, at elevated temperature, such as 80-90°C, preferably about 82°C.

20 According to a further process, (H), compounds of formula (I) wherein R^8 represents substituted or unsubstituted 1,2,5-triazine may be prepared by reaction of an intermediate of formula (X) with a dicarbonyl compound of formula (XI):



(X)



(XI)

- 25 -

wherein R^1 , R^2 , R^4 , R^5 , X, Y and n are as defined for formula (I) and R^{35} and R^{36} each independently represent H or a suitable substituent such as C_{1-6} alkyl, e.g. methyl.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, conveniently at ambient temperature.

Further details of suitable procedures will be found in the accompanying Examples.

Compounds of formula (VIII) may be prepared as described in J. Med. Chem., 27, (1984), 849.

Compounds of formula (I) may also be prepared from other compounds of formula (I) using suitable interconversion procedures. For example, compounds of formula (I) wherein Y represents C_{1-4} alkyl substituted by an aromatic heterocycle may be prepared from compounds of formula (I) wherein Y represents C_{1-4} alkyl substituted by oxo by reduction, for example, using borane. Suitable interconversion procedures are described in the accompanying Examples, or will be readily apparent to those skilled in the art.

Intermediates of formula (III) may be prepared from intermediates of formula (II) by reaction with a compound of formula $Hal-Y-CO_2R^{30}$, where Hal represents halo such as chloro, bromo or iodo and R^{30} and Y are as above defined, in the presence of a base. Suitable bases include tertiary amines, for example, triethylamine. Conveniently the reaction is effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, at elevated temperature, such as the reflux temperature of the solvent.

Intermediates of formula (IV) are commercially available or may be prepared from commercially available materials by conventional procedures well-known to those skilled in the art.

- 26 -

Intermediates of formula (II) may be prepared as described in published European patent application no. 0 528 495.

5 Intermediates of formula (V) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-Y-CN, wherein Hal is halo such as bromo, chloro or iodo and Y is as previously defined.

10 Intermediates of formula (VI) may be prepared from intermediates of formula (V) by treatment with an alkylthioamide, such as, for example, thioacetamide.

15 Intermediates of formula (VII) may be prepared from intermediates of formula (III) by treatment with hydrazine. The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, for example, ethanol, at elevated temperature.

20 Intermediates of formula (IX) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-Y-C(NH)NH₂, where Hal and Y are as previously defined.

25 Intermediates of formula (X) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-Y-C(NH)NHNH-Boc, wherein Hal and Y are as previously defined and Boc stands for t-butoxycarbonyl, followed by deprotection under acidic conditions.

Compounds of formula (XI) are commercially available or may be prepared from commercially available compounds by known methods.

30 Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

- 27 -

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, any suitable intermediates may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation or separation by fractional crystallization and removal of the chiral auxiliary. The diastereomeric intermediates can then be used to prepare optically pure compounds of formula (I).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an IC₅₀ value for the test compound. The compounds of Examples 1-10, for example, were found to have IC₅₀ values less than 500nM.

- 28 -

DESCRIPTION 1: cis-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine hydrochloride salt

5 a) A solution of methyl 4-nitrobutyrate (23g) and benzaldehyde (16ml) in acetic acid (39ml) containing ammonium acetate (12.12g) was heated at reflux under nitrogen for 2h. The reaction mixture was cooled to 5°C, whereby a pale-yellow solid crystallised. This was isolated by filtration, then dissolved in dichloromethane, washed cautiously with saturated aqueous sodium bicarbonate solution (2 x), then dried (MgSO₄) and
10 concentrated to leave a yellow solid. Recrystallisation from ethyl acetate provided 5-nitro-2-oxo-6-phenylpiperidine (12.5g) as a crystalline, white solid. ¹H NMR (CDCl₃) δ 7.46-7.26 (m), 6.0 (br s), 5.24 (dd, J = 1.4, 7.0Hz), 4.70 (m), 2.70-2.50 (m), 2.38-2.24 (m).

15 b) Potassium *t*-butoxide (1.68g) was added to a solution of 5-nitro-2-oxo-6-phenylpiperidine (3g) in a mixture of dichloromethane (50ml) and methanol (50ml) and the mixture was cooled to -78°C under nitrogen. Ozone was bubbled through the solution for 3h. A yellow-green solution resulted, and TLC
20 indicated no starting material remained. The reaction mixture was purged with oxygen for 5 min to remove excess ozone, then dimethylsulfide (7ml) was added and the reaction mixture was allowed to warm to 23°C. The solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane and
25 water. The layers were separated, and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with brine, then dried (K₂CO₃) and concentrated to leave a yellow solid.

30 This crude material was slurried in dry tetrahydrofuran and added to lithium aluminium hydride (1M in THF, 50ml) then heated at reflux for 12h. After cooling to 23°C, the reaction

- 29 -

mixture was quenched by the cautious addition of water (dropwise) under nitrogen, then 2M sodium hydroxide. The mixture was filtered through a pad of Hyflo, the filtrate was washed with brine, then dried (K_2CO_3) and concentrated to leave a yellow solid. Purification by silica-gel chromatography ($CH_2Cl_2/MeOH/NH_3$ 97:3:1 then $CH_2Cl_2/MeOH$ 95:5) provided 3-hydroxy-2-phenylpiperidine as a ca 4:1 mixture of *cis*- and *trans*-isomers respectively. 1H NMR ($CDCl_3$) 7.44-7.20 (m), 3.84 (2), 3.76 (s), 3.54 (m), 3.4 (s), 3.3 (d, $J = 8Hz$), 3.26 (m), 3.04 (m), 2.78 (ddd, $J = 2.9, 11.9, 11.9Hz$), 2.70 (ddd, $J = 2.9, 11.9, 11.9Hz$), 2.18-1.78 (m), 1.48 (m). MS (EI) m/z 177 (M^+).

c) Di-*t*-butyldicarbonate (1.36g) was added to a solution of 3-hydroxy-2-phenylpiperidine (1g) in dichloromethane (8ml) under nitrogen and the mixture stirred at 23°C for 3h. The solvent was removed *in vacuo*, and the residue purified by silica-gel chromatography ($CH_2Cl_2/MeOH/NH_3$ 97:3:0.5) to provide *cis*- and *trans*-1-*t*-butyloxycarbonyl-3-hydroxy-2-phenylpiperidine (1.4g) as a clear, viscous oil. 1H NMR ($CDCl_3$) d 7.50-7.42 (m), 7.40-7.14 (m), 5.36 (d, $J = 5.6Hz$), 4.50 (m), 4.44 (m), 4.12-3.92 (m), 3.02 (ddd, $J = 3.0, 12.5, 12.5Hz$), 2.87 (ddd, $J = 3.0, 12.5, 12.5Hz$), 1.88-1.66 (m), 1.46 (s), 1.36 (s).

d) To a cooled (0°C) solution of 1-*t*-butyloxycarbonyl-3-hydroxy-2-phenylpiperidine (1.4g) in dry dimethylformamide (5ml) was added sodium hydride (80% dispersion in mineral oil; 182mg). The cooling bath was removed and the reaction mixture stirred at 23°C for 30 min. A solution of 3,5-bis(trifluoromethyl)benzyl bromide (1.87g) in dry dimethylformamide (1ml) was added and stirring was continued for 2h at room temperature. The mixture was diluted with water (100ml) and extracted with ethyl acetate (3 x 40ml). The combined organic extracts were washed with brine (1 x 30ml),

- 30 -

dried (MgSO_4) and evaporated to yield a pale yellow oil. Purification by chromatography on silica using gradient elution of hexane in ethyl acetate (9:1 - 4:1) afforded the product cis-1-*t*-butyloxycarbonyl-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine (350mg) as an oil. ^1H NMR (250MHz, CDCl_3) δ 7.77 (1H, s, ArH), 7.71 (2H, s, ArH), 7.53-7.57 (2H, m, ArH), 7.2-7.4 (3H, m, ArH), 5.70 (1H, br d, app. $J = 7.0\text{Hz}$, NCHPh), 4.73 (2H, brs, OCH_2), 3.84-3.98 (2H, m, NCHCHO + NCHH), 2.77 (1H, ddd, $J = 13.0, 13.0, 3.0\text{Hz}$, NCHH), 2.00 (2H, mc, CH_2), 1.6-1.8 (2H, m, CH_2), 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$).

e) Trifluoroacetic acid (3ml) was added to the product of (d) above (800mg) under nitrogen and the resulting solution was stirred for 1h. Excess trifluoroacetic acid was removed *in vacuo* and the residue was partitioned between 2M sodium hydroxide and dichloromethane. The organic phase was washed with brine, dried (MgSO_4) and evaporated to afford a colourless oil. Purification on silica (dichloromethane in methanol, 98:2 - 95:5) afforded the product cis-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine (360mg) as a colourless oil. ^1H NMR (360MHz, CDCl_3) δ 7.78 (1H, s, ArH), 7.44 (2H, s, ArH), 7.18-7.38 (5H, s, ArH), 4.52 (1H, d, $J = 12.5\text{Hz}$, OCHH), 4.13 (1H, d, $J = 12.5\text{Hz}$, OCHH), 3.84 (1H, d, $J = 1.0\text{Hz}$, NCHPh), 3.68 (1H, d, $J = 1.5\text{Hz}$), 3.28 (1H, m, NCHCHO), 2.84 (1H, ddd, $J = 3.0, 12.5, 12.5\text{Hz}$, NCHH), 2.20 (1H, mc, NCHH), 1.8-1.98 (2H, m, CH_2), 1.64-1.78 (1H, m, CHH), 1.50-1.58 (1H, m, CHH); MS m/z 404 ($(\text{M}+1)^+$, 90%).

The oil was dissolved in ether to which was added excess ethereal hydrogen chloride. Upon standing a white solid crystallised. This was filtered and recrystallised from ethyl acetate-methanol to afford the title compound as white crystals:

- 31 -

mp 200-203°C. ¹H NMR (360MHz, DMSO) δ 7.95 (1H, s, ArH), 7.81 (2H, s, ArH), 7.37-7.47 (5H, m, ArH), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.56 (1H, s, NCHPh), 4.32 (1H, d, J = 13.0Hz, OCHH), 3.96 (1H, s, NCHCHO), 3.10 (1H, t, J = 13.0Hz, NCHH), 2.23 (1H, d, J = 13.0Hz, NCHH), 1.64-2.00 (4H, m, CH₂ x 2); MS (CI⁺) m/z 404 ((M+1)⁺, 90%); Found: C, 54.08; H, 4.47; N, 3.13. Calcd. for C₂₀H₂₀F₆NOCl.0.25H₂O: C, 54.06; H, 4.65; N, 3.15%.

10 DESCRIPTION 2: (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carbomethoxy)methyl-2-phenylpiperidine

cis-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine hydrochloride (Description 1, 1g) was liberated from the hydrochloride salt by partitioning between ethyl acetate and 2M sodium hydroxide. The organic phase was washed successively with water, saturated brine, dried (MgSO₄) and evaporated *in vacuo*. To a solution of the residual oil in tetrahydrofuran (20ml) was added triethylamine (0.4ml) and methyl bromoacetate (400mg) and the solution was heated at reflux under an atmosphere of nitrogen for 16h. To the cooled solution was added ethyl acetate and water and the organic phase washed further with water and dried (MgSO₄). After the solvent had been removed *in vacuo* the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (3:10). The product was recrystallised from diethyl ether/petroleum ether to give the title compound: mp 81-83°C. Found: C, 57.35; H, 4.98; N, 2.84; C₂₃H₂₃F₆NO₃.0.1(H₂O) requires C, 57.71; H, 4.86; N, 2.93%. MS (CI⁺) m/z 476 (M+H)⁺.

30

- 32 -

DESCRIPTION 3: (+)-(2S,3S)-cis-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine hydrochloride salt

5 a) The mixture of *cis*- and *trans*-isomers of 3-hydroxy-2-phenylpiperidine (Description 1, (2b)) and 4-toluenesulfonic acid monohydrate was crystallized from methanol/ethyl acetate to give *cis*-3-hydroxy-2-phenylpiperidinium tosylate: mp 266-267°C.

10 b) The tosylate salt (Description 3(a) above) was dissolved in a mixture of ethyl acetate and 10% aqueous Na₂CO₃ with warming. The organic phase was washed with saturated brine, dried (K₂CO₃) and evaporated to give crystalline *cis*-3-hydroxy-2-phenylpiperidine, mp 110-110.5°C.

15 c) *cis*-3-Hydroxy-2-phenylpiperidine (Description 3b) and (-)-dibenzoyltartrate were dissolved in methanol and crystallized by addition of ethyl acetate. The solid was recrystallised from hot methanol to give the hemi dibenzoyltartrate salt: mp 223-224°C. This was liberated from the salt as described above to give the single enantiomer (+)-*cis*-3-hydroxy-2-phenylpiperidine, mp 93-95°C. [α]_D²³ = +98.5° (c=1, MeOH).
20 The mother liquors were converted to the free base as described in Description 3b and crystallization using (+)-dibenzoyltartrate in an analogous manner to that described above gave (-)-3-hydroxy-2-phenylpiperidine, mp 93-95°C. [α]_D²³ = -97.2° (c=1, MeOH).

25 d) (+)-*cis*-3-Hydroxy-2-phenylpiperidine was reacted according to the procedure detailed in Description 1c-e to give (+)-*cis*-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine hydrochloride as a crystalline solid: mp 215-216°C. [α]_D = +87.3° (c=1, MeOH). ¹H NMR (360MHz, DMSO-d₆) δ 7.95 (1H, s, ArH), 7.81 (1H, s, ArH), 7.47 (2H, m, ArH), 7.37 (3H, m, ArH), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.56
30

- 33 -

(1H, s, NCHPh), 4.32 (1H, d, J = 13.0Hz, OCHH), 3.96 (1H, s, NCHCHO), 3.10 (1H, t, J = 13.0Hz, NCHH), 2.23 (1H, d, J = 13.0Hz, NCHH), 2.00-1.64 (4H, m, CH₂ x 2); MS (CI⁺) m/z 404 (M+1⁺, 90%); Found: C, 54.52; H, 4.60; N, 3.11. Calcd. for C₂₀H₁₉F₆NO.HCl: C, 54.62; H, 4.58; N, 3.18%.

DESCRIPTION 4: (+)-(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carbomethoxy)methyl-2-phenylpiperidine

The title compound was prepared from (+)-cis-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine (Description 3) using the procedure detailed in Description 2: mp 60-70°C. [α]_D = +132.3° (c=1, MeOH). ¹H NMR (360MHz, CDCl₃) d 1.57-1.63 (3H, m, CH₂ + CHH), 2.04-2.17 (2H, m, CHH, CHHN), 3.07-3.10 (1H, m, NCHCHO), 3.20 (1H, d, J = 17.0Hz, NCHHCO₂CH₃), 3.31 (1H, d, J = 17.0Hz, NCHHCO₂CH₃), 3.58 (3H, s, CH₃), 3.93 (1H, s, NCHPh), 4.07 (1H, d, J = 12.0Hz, OCHH), 4.49 (1H, d, J = 12.0Hz, OCHH), 7.28-7.34 (3H, m, ArH), 7.43-7.45 (2H, m, ArH), 7.54 (2H, s, ArH), 7.71 (1H, s, ArH). MS (CI⁺) m/z 476 (M+1⁺, 100%). Found: C, 58.31; H, 4.90; N, 2.94. Calcd. for C₂₃H₂₃F₆NO₃: 58.11; H, 4.88; N, 2.95%.

DESCRIPTION 5: (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(cyanomethyl)-2-phenylpiperidinium hydrochloride

The compound of Description 1 (5g), potassium carbonate (1.7g) and bromoacetonitrile (0.87ml) were suspended in dimethylformamide (15ml) and the mixture was stirred under nitrogen at 60°C for 3 h. The mixture was cooled, diluted with water (200ml) and extracted with ethyl acetate (2 x 50ml). The organic extracts were washed with brine, dried (MgSO₄) and

- 34 -

evaporated, affording a brown oil. This was purified on silica using ethyl acetate in petrol (10%) as eluant. This afforded the product as a colourless oil. The hydrochloride salt was prepared by dissolution in ethereal hydrogen chloride and the salt was recrystallised from ether-hexane: mp 133-134°C. ¹H NMR (360MHz, CDCl₃) δ 1.75 (2H, mc, CHH), 1.90 (2H, mc, CHH), 2.31 (1H, mc, CHH), 2.71 (1H, mc, CHH), 3.19 (1H, mc, CHHN), 3.72 (1H, mc, CHHN), 3.81 (1H, d, J = 17.5Hz, NCHHCN), 3.86 (1H, s, CHO), 4.02 (1H, d, J = 17.5Hz, NCHHCN), 4.09 (1H, s, CHPh), 4.35 (1H, d, J = 13.0Hz, OCHH), 4.73 (1H, d, J = 13.0Hz, OCHH), 7.4 (3H, mc, ArH), 7.69-7.73 (5H, m, ArH); MS (Cl⁺) m/z 443 (M⁺+1, 30%). Found: C, 54.87; H, 4.30; N, 5.66. Calcd. for C₂₂H₁₈F₆N₂O.HCl : C, 55.18; H, 4.42; N, 5.85%.

15 DESCRIPTION 6: (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(thiocarboxamidomethyl)piperidine

The compound of Description 5 (1g) was dissolved in dimethylformamide (anhydrous, 10ml) and the solution was saturated with dry hydrogen chloride gas. The reaction was heated to 100°C under nitrogen and thioacetamide (0.34g) was added; this mixture was allowed to stir at 100°C for 3h. Dimethylformamide was removed *in vacuo*. The residue was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, brine, dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil. This was purified on silica using a gradient elution of ethyl acetate in petrol (10-50%). The product was further purified by recrystallisation from ethyl acetate-petrol: mp 164-166°C; ¹H NMR (360MHz, CDCl₃) δ 1.56-1.70 (2H, m, CH₂), 1.96-2.10 (1H, m, CHH), 2.15-2.32 (2H, m, CHHN + CHH), 2.98-3.06 (1H, bd, NCHH), 3.09 (1H, d, J = 18.0Hz, CHHSNH₂), 3.50 (1H, d, J = 18.0Hz,

- 35 -

5 NCHHCSNH₂), 3.50 (1H, s, CHO), 3.60 (1H, s, NCHPh), 4.04 (1H, d, J = 12.0Hz, OCHHAr), 4.47 (1H, d, J = 12.0Hz, OCHHAr), 7.26-7.36 (5H, m, CHPh), 7.53 (2H, s, Ar-H), 7.75 (H, s, Ar-H), 7.61 (1H, bs, NHH), 8.99 (1H, bs, NHH); MS (CI⁺) m/z 477 (M⁺+1, 15%); Found: C, 55.09; H, 4.58; N, 5.97. Calc for C₂₂H₂₂F₆N₂OS : C, 55.46; H, 4.65; N, 5.88.

10 DESCRIPTION 7: (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carboxyhydrazidomethyl)-2-phenylpiperidinium hydrochloride

Hydrazine hydrate (3.0ml) was added to a solution of the compound of Description 2 (2.95g) in ethanol (80ml). The solution was heated at reflux for 18h after which the ethanol was removed *in vacuo*. The residue was extracted into ethyl acetate and the organic layer was washed with brine, dried (MgSO₄) and concentrated to give the title compound (2.79g). This was dissolved in methanol (5ml) and a methanolic solution of hydrogen chloride was added. Methanol was removed *in vacuo* and the salt was recrystallised from diethyl ether to give the hydrochloride salt. ¹H NMR (360MHz, DMSO) δ 1.77-1.93 (2H, m, CH₂), 2.08-2.21 (1H, m, CH₂), 2.22-2.35 (1H, m, CH₂), 3.56 (1H, d, NCHHCH₂), 3.64 (1H, d, J = 16.5Hz, NCHHCO), 3.77 (1H, d, NCHHCH₂), 3.92 (1H, d, J = 16.5Hz, NCHHCO), 3.96 (1H, brs, CHO), 4.37 (1H, d, J = 13.0Hz, OCHH), 4.83 (1H, d, J = 13.0Hz, OCHH), 4.95 (1H, s, CHPh), 7.36-7.46 (3H, m, ArH), 7.53-7.62 (2H, brs, ArH), 7.95 (2H, s, ArH), 7.97 (1H, s, ArH); MS (CI)⁺ m/z 475.

30 DESCRIPTION 8: (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carboxyhydrazidomethyl)-2-phenylpiperidinium hydrochloride

- 36 -

The title compound was prepared according to the procedure outlined in Description 7 using the compound of Description 4 as a starting material. ¹H NMR (360MHz, DMSO) d 1.77-1.93 (2H, m, CH₂), 2.08-2.21 (1H, m, CH₂), 2.22-2.35 (1H, m, CH₂), 3.56 (1H, d, NCHHCH₂), 3.64 (1H, d, J = 16.5Hz, NCHHCO), 3.77 (1H, d, NCHHCH₂), 3.92 (1H, d, J = 16.5Hz, NCHHCO), 3.96 (1H, brs, CHO), 4.37 (1H, d, J = 13.0Hz, OCHH), 4.83 (1H, d, J = 13.0Hz, OCHH), 4.95 (1H, s, CHPh), 7.36-7.46 (3H, m, ArH), 7.53-7.62 (2H, brs, ArH), 7.95 (2H, s, ArH), 7.97 (1H, s, ArH); MS (CI)⁺ m/z 475.

DESCRIPTION 9: (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(cyanomethyl)-2-phenylpiperidine

The title compound was prepared from the reaction of bromoacetonitrile and the compound of Description 3 according to the procedure detailed in Description 5. Purification by chromatography on silica using 10% hexane in ethyl acetate afforded the product as a colourless oil. ¹H NMR (360MHz, CDCl₃) d 1.75 (2H, mc, CH₂CH₂N), 2.14 (2H, mc, CH₂CH₂N), 2.63-2.74 (1H, m, CHHN), 2.96-3.06 (1H, m, CHHN), 3.35 (1H, d, J=17.0Hz, CHHCN), 3.48 (1H, d, J=2.0Hz, CHO), 3.55 (1H, d, J=17.0Hz, CHHN), 3.64 (1H, d, J=2.0Hz, CHPh), 4.07 (1H, d, J=12.0Hz, OCHH), 4.52 (1H, d, J=12.0Hz, OCHH), 7.28-7.38 (3H, m, ArH), 7.4-7.48 (2H, m, ArH), 7.56 (2H, m ArH), 7.73 (1H, m, ArH).

DESCRIPTION 10: (2S,3S)-3-((3-*t*-Butyl-5-methylphenyl)methoxy)-2-phenylpiperidine

This compound was prepared from the compound of Description 3c and 3-*t*-butyl-5-methylbenzyl bromide, following the procedure described in Descriptions 1c-e. mp 180-182°C. MS

- 37 -

(CI⁺) m/z 338 (M⁺+1, 100%). Found: C, 73.81; H, 8.63; N, 3.74.
Calcd. for C₂₃H₃₁NO.HCl: C, 73.87; H, 8.62; N, 3.75%.

DESCRIPTION 11: (2S,3S)-3-((3,5-Dichlorophenyl)methoxy)-2-phenylpiperidine

5 This compound was prepared from the compound of Description 3c and 3,5-dichlorobenzyl chloride, following the procedure described in Descriptions 1c-e. ¹H NMR (CDCl₃) δ 1.49-1.53 (1H, m, CHH), 1.60-1.70 (1H, m, CHH), 1.82-1.95 (1H, m, CHH), 2.14-2.18 (1H, m, CHH), 2.79-2.87 (1H, m, NCHH), 3.27-3.31 (1H, m, NCHH), 3.60 (1H, s, CHO), 3.82 (1H, s, CHPh), 4.02-4.05 (1H, d, J=13Hz, OCHH), 4.31-4.35 (1H, d, J=13Hz, OCHH), 6.80 (2H, s, ArH), 7.15 (1H, s, ArH), 7.25-7.35 (5H, m, ArH). Found: C, 58.24; H, 5.38; N, 3.91. Calcd. for C₁₈H₁₉Cl₂NO.HCl: C, 58.01; H, 5.41; N, 3.76%.

DESCRIPTION 12: (2S,3S)-3-((3-Chloro-5-methylphenyl)methoxy)-2-phenylpiperidine

20 This compound was prepared from the compound of Description 3c and 3-chloro-5-methylbenzyl bromide, following the procedure described in Descriptions 1c-e: mp 235-237°C. MS (CI⁺) m/z 316 (M⁺+H, 100%). Found: C, 64.68; H, 6.50; N, 3.98. Calcd. for C₁₉H₂₂ClNO.HCl: C, 64.78; H, 6.58; N, 3.98%.

DESCRIPTION 13: (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-(diphenylmethyl)pyrrolidinium hydrochloride

(a) N-t-Butyloxycarbonyl-(S)-diphenylalanyl

30 A solution of methyl sulfoxide (4.4ml) in dichloromethane (13ml) was added dropwise to a cooled (-78°C) solution of oxalyl chloride (4ml) in dichloromethane (50ml). After 15 min, a solution of N-t-butyloxycarbonyl-(S)-diphenylalanyl (10g) in

- 38 -

dichloromethane (150ml) was added dropwise at -30°C. The solution was allowed to stir for 30 min, triethylamine (17ml) was added and the solution was allowed to warm to -10°C. Ice-water (200ml) was added to the solution which was then poured
5 onto hexane (600ml). The organic phase was separated, washed successively with citric acid (200ml), saturated aqueous sodium bicarbonate (2 x 150ml), brine (1 x 150ml) then dried (MgSO₄) and concentrated *in vacuo* to leave a white crystalline solid. ¹H NMR (250MHz, CDCl₃) δ 1.42 (9H, s, C(CH₃)₃), 4.48 (1H, d),
10 4.86 (1H, d), 5.10 (1H, t), 7.26 (10H, m, ArH), 9.6 (1H, s, CHO).

(b) N-*t*-Butyloxycarbonyl-1-(diphenylmethyl)-2-hydroxypent-4-enyl-1-amine

A solution of N-*t*-butyloxycarbonyl-(S)-diphenylalanal (10.9g) in tetrahydrofuran (60ml) was added dropwise to a
15 solution of allyl magnesium chloride (2M in tetrahydrofuran, 36ml) at -10°C. After 30 min the mixture was poured onto ice-cold saturated aqueous ammonium chloride and the resulting mixture was extracted with ethyl acetate (3 x 150ml). The combined organic extracts were washed with brine (1 x 100ml),
20 then dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using hexane in ethyl acetate (gradient elution of 9:1 to 4:1) as eluant to afford the compound as a white solid. ¹H NMR (360MHz, CDCl₃) δ 1.42 (9H, s, (CH₃)₃), 2.22 (2H, m), 2.68 (3H, brs), 3.48 (t), 3.57 (1H, m),
25 3.86 (1H, s), 4.07 (d, J = 11Hz), 5.04 (1H, m), 5.71 (1H, m), 6.97-7.36 (10H, m, ArH).

(c) 2-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-N-*t*-butyloxycarbonyl-1-(diphenylmethyl)-pent-4-enyl-1-amine

Sodium hydride (80% in oil, 0.53g) was added to a
30 solution of 3,5-bis(trifluoromethyl)benzyl bromide (5ml) and the compound of (13b) above (5g) in dimethylformamide (8ml). After

- 39 -

stirring for 1h water (80ml) was added and the mixture was extracted with ethyl acetate (3 x 100ml). The combined organics extracts were washed with brine (1 x 100ml) then dried (MgSO₄) and concentrated to leave an oil which was purified on silica using hexane in ethyl acetate as eluant (gradient elution of 97:3 to 4:1). This afforded the title compound as a colourless oil. ¹H NMR (360MHz, CDCl₃) δ 1.25 (s), 1.30 (s), 2.35 (m), 3.31 (m), 3.40 (dd, J = 5.2, 8.3Hz), 3.97 (d), 4.27 (d), 4.38 (m), 4.65 (m), 4.85 (d), 5.16-5.02 (m), 5.77 (m), 7.35-7.13 (m), 7.76 (s), 7.85 (s).

(d) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy-2-(diphenylmethyl)pyrrolidinium hydrochloride

A solution of the compound of (c) above (5.2g) in dichloromethane (40ml) and methanol (40ml) was treated with a stream of ozone in oxygen at -78°C for 1h. Methyl sulfide (3ml) was added and the mixture was warmed to 23°C and concentrated *in vacuo*. The residue was dissolved in chloroform (50ml), triethylsilane (5.6ml) was added followed by dropwise addition of a solution of trifluoroacetic acid (6.9ml) in chloroform (5ml). After 1h the solvent was evaporated *in vacuo* and trifluoroacetic acid (10ml) was added to the residue. After stirring for 30 min the mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried (K₂CO₃) and concentrated to leave a brown oil. This was purified on silica gel eluting with dichloromethane/methanol (99:1) to provide the title compound as the free base. This was converted to the salt by treatment with methanolic hydrogen chloride: mp >230°C. [α]_D²⁵ = +46.6° (c=1, CH₃OH). Found: C, 59.95; H, 4.74; N, 2.63%. Calcd. for C₂₆H₂₃F₆NO.HCl.0.2H₂O: C, 60.11; H, 4.73; N, 2.70%.

- 40 -

DESCRIPTION 14: (2R,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-(diphenylmethyl)pyrrolidinium hydrochloride

The title compound was prepared from N-*t*-butyloxycarbonyl-(R)-diphenylalanol by a procedure analogous to that described in Description 13: mp > 230°C. $[\alpha]^{23}_D = +12.1^\circ$ (c=1, CH₃OH).

DESCRIPTION 15: (2S,3S)-3-((3,5-Dichlorophenyl)methoxy)-2-(diphenylmethyl)pyrrolidinium hydrochloride

(a) N-*t*-Butyloxycarbonyl-2-((3,5-dichlorophenyl)methoxy)-1-(diphenylmethyl)pent-4-enyl-1-amine

The compound of Description 13b was alkylated with 3,5-dichlorobenzyl chloride by a procedure analogous to that described in Description 13c, to afford the title compound as an oil. ¹H NMR (360MHz, CDCl₃) δ 1.25 (9H, s), 2.41-2.27 (2H, m), 3.32 (1H, m), 4.07 (1H, d, J=11Hz), 4.13 (1H, d, J=12Hz), 4.30 (1H, d, J=12Hz), 4.65 (2H, m), 5.13 (2H, m), 5.76 (1H, m), 7.35-6.60 (13H, m). MS (CI⁺) m/z 526, 528 (M⁺+1, 100%, 80%).

(b) (2S,3S)-3-((3,5-Dichlorophenyl)methoxy)-2-(diphenylmethyl)pyrrolidinium hydrochloride

The compound of Description 15a above was treated with ozone followed by triethylsilane-trifluoroacetic acid by a procedure analogous to that described in Description 13d to afford the title compound as a white crystalline solid: mp>230°C. Found: C, 64.52; H, 5.34; N, 3.12. Calcd. for C₂₄H₂₃Cl₂NO.HCl: C, 64.23; H, 5.39; N, 3.12%.

DESCRIPTION 16: (2S,3S)-3-((3-*t*-Butyl-5-chlorophenyl)methoxy)-2-phenylpiperidinium hydrochloride

(a) 4-*t*-Butyl-2-chloro-6-(methylthiomethyl)aniline

- 41 -

4-*t*-Butyl-2-chloroaniline (30g) was dissolved in dichloromethane (1.2l) and the solution was cooled to -5°C. N-chlorosuccinimide (21.7g) was added portionwise to the vigorously stirred solution and stirring was continued for 1h. Dimethyl sulfide (35ml) was added to the solution (-5°C) and stirring was continued for a further 1h. The solution was then cooled to -65°C and triethylamine (27ml) was added. This solution was allowed to warm to room temperature overnight. The solution was evaporated to half volume, washed with sodium hydroxide (1N), water and brine successively. The organic solution was dried and evaporated and the residue was purified on silica using hexane to 3% ether in hexane as eluant. This afforded the product (31.2g) as a red oil. ¹H NMR (CDCl₃, 250MHz) δ 1.27 (9H, s, (CH₃)₃), 1.99 (3H, s, SCH₃), 3.69 (2H, s, CH₂SCH₃), 4.38 (2H, br s, NH₂), 6.92 (1H, d, J=2.0Hz, ArH), 7.21 (1H, d, J=2.0Hz, ArH). MS (CI⁺) m/z 244 (M⁺+1, 100%).

(b) 4-*t*-Butyl-2-chloro-6-methylaniline

4-*t*-Butyl-2-chloro-6-(methylthiomethyl)aniline (1.3g) was dissolved in methanol (50ml) and Raney nickel (prewashed to pH 7) was added portionwise until t.l.c. indicated all starting material had reacted (ether-hexane, 1:10). The Raney nickel was removed by filtration through celite and the filtrate was evaporated. The residue was dissolved in ether and washed with brine, dried (MgSO₄) and evaporated. The residue was purified on silica using hexane - 5% ether in hexane as eluant to afford the product as a yellow liquid. ¹H NMR (360MHz, CDCl₃) δ 1.26 (9H, s, (CH₃)₃), 2.19 (3H, s, CH₃), 3.97 (2H, s, NH₂), 6.97 (1H, d, J=2.0Hz, ArH), 7.14 (1H, d, J=2.0Hz, ArH).

(c) 3-*t*-Butyl-5-chlorotoluene

4-*t*-Butyl-2-chloro-6-methylaniline (1.97g) was dissolved in ethanol (50ml); sulphuric acid (1.88ml, conc.) was added

- 42 -

dropwise and the resulting blue solution was heated at reflux. Sodium nitrite (1.72g) was added portionwise over 30 min. The resulting mixture was heated at reflux for a further 30 min, then cooled and was poured onto ice-water and extracted with ether (2 x 50ml). The ethereal extract was dried (MgSO₄) and evaporated and the residue was purified on silica gel using hexane as eluant. This afforded the product as a colourless oil. ¹H NMR (360MHz, CDCl₃) δ 1.29 (9H, s, (CH₃)₃), 2.31 (3H, s, CH₃), 6.98 (1H, brs, ArH), 7.05 (1H, brs, ArH), 7.15 (1H, brs, ArH). MS (CI-) m/z 181 (M⁺-H, 100%).

(d) 3-*t*-Butyl-5-chlorobenzyl bromide

3-*t*-Butyl-5-chlorotoluene (5.7g) was dissolved in carbon tetrachloride (80ml) and N-bromosuccinimide (5.56g) was added followed by benzoyl peroxide (750mg). This mixture was heated at reflux for 6h. The mixture was cooled, filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica using hexane as eluant. This afforded the title compound as a colourless liquid. ¹H NMR (360MHz, CDCl₃) δ 1.31 (9H, s, (CH₃)₃), 4.42 (2H, s, CH₂), 7.20 (1H, t, J=1.5Hz, ArH), 7.26 (1H, t, J=1.5Hz, ArH), 7.28 (1H, t, J=1.5Hz, ArH).

(e) (2S,3S)-1-*t*-Butyloxycarbonyl-3-((3-*t*-butyl-5-chlorophenyl)methoxy)-2-phenylpiperidine.

(+)-*cis*-3-Hydroxy-2-phenylpiperidine (Description 3c) was reacted with 3-*t*-butyl-5-chlorobenzyl bromide (Description 15d above) according to the procedure detailed in Description 1c-d to afford the title compound. ¹H NMR (360MHz, CDCl₃) δ 1.27 (9H, s, C(CH₃)₃), 1.46 (9H, s, C(CH₃)₃), 1.52-1.66 (2H, m), 1.8-2.0 (2H, m), 2.69 (1H, td, J=3.5Hz, 13.0Hz, NCHH), 3.81 (1H, q, J=5Hz, NCHH), 3.92 (1H, brd, CHO), 4.60 (2H, q, J=12Hz, OCH₂), 5.70 (1H, brs, CHPh), 7.10 (1H, s, ArH), 7.18 (1H, s,

- 43 -

ArH), 7.22 (2H, s, ArH), 7.43-7.47 (2H, m, ArH), 7.57-7.59 (2H, m, ArH).

(f) The compound of Description 15e above was dissolved in methanolic hydrogen chloride overnight. The solution was then concentrated *in vacuo* and the residue triturated with ether. This afforded the title compound as a white crystalline powder: mp 210-211°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.21 (9H, s, C(CH₃)₃), 1.66-1.80 (2H, m, CH₂), 1.86-1.93 (1H, m, CHH), 2.18-2.22 (1H, m, CHH), 3.04-3.11 (1H, m, NCHH), 3.3 (1H, m, NCHH), 3.88 (1H, brs, CHO), 4.14 (1H, d, J=12Hz, OCHH), 4.52 (1H, s, CHPh), 4.53 (1H, d, J=12Hz, OCHH), 6.95 (1H, s, ArH), 7.00 (1H, s, ArH), 7.24 (1H, t, J=1.8Hz, ArH), 7.3-7.5 (5H, m, ArH), MS (CI⁺) m/z 358 (M⁺+1, 100%). Found: C, 66.68; H, 7.29; N, 3.40. Calcd. for C₂₂H₂₈ClNO.HCl: C, 67.00; H, 7.41; N, 3.55%.

DESCRIPTION 17: (2R*,3R*)-3-((3-Carbomethoxyphenyl)methyloxy)-2-phenylpiperidine

(a) (2R*,3R*)-1-*t*-Butyloxycarbonyl-3-((3-cyanophenyl)methyloxy)-2-phenylpiperidine

This compound was prepared from 1-*t*-butyloxycarbonyl-3-hydroxy-2-phenylpiperidine (Description 1c) and α-bromo-m-tolunitrile according to the procedure described in Example 1d. ¹H NMR (360MHz, CDCl₃) δ 1.49 (9H, s, (CH₃)₃), 1.6-1.72 (2H, m), 1.87-1.99 (2H, m), 2.72 (1H, dt, J = 13, 4Hz, NCHH), 3.80-3.95 (2H, m, CHO + NCHH), 4.65 (2H, q, J = 12Hz, OCH₂), 5.69 (1H, brs, CHPh), 7.1-7.5 (9H, m, ArH).

(b) (2R*,3R*)-3-((3-Carbomethoxyphenyl)methyloxy)-2-phenylpiperidine

The compound of (a) above (1.5g) was dissolved in methanol (15ml) and concentrated hydrochloric acid (aqueous, 10ml) was

- 44 -

added. The contents were heated at reflux for 12h. The solution was cooled and evaporated to leave a brown oil. This was dissolved in methanolic hydrogen chloride and the resulting solution was stirred overnight, then evaporated. The residue was purified by dispersion between water and ethyl acetate and the organic layer was dried (MgSO_4) and concentrated. The residue was purified by chromatography on silica using a gradient elution of 2%-6% methanol in dichloromethane. The first compound to elute was characterised as the hydrochloride salt by dissolution in methanolic hydrogen chloride. The salt was recrystallised from ethyl acetate methanol: mp 206-208°C.

(c) (2R*,3R*)-3-((3-(Carbomethoxy)phenyl)methyloxy)-2-phenylpiperidine

^1H NMR (CDCl_3) δ 1.45-1.71 (2H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.83-2.02 (1H, m, NCH_2CHH), 2.12-2.23 (1H, m, NCH_2CHH), 2.44 (1H, bs, NH), 2.77-2.90 (1H, m, NCHH), 3.24-3.34 (1H, m, NCHH), 3.61-3.66 (1H, bs, CHO), 3.8-3.83 (1H, d, $J = 15\text{Hz}$, CHPh), 3.90 (3H, s, COOCH_3), 4.15 (1H, d, $J=12\text{Hz}$, OCHH), 4.39 (1H, d, $J=12\text{Hz}$, OCHH), 7.09 (7H, m, ArH), 7.71 (1H, bs, ArH), 7.83-7.89 (1H, m, ArH); MS (CI^+) m/z 326 (M^++1 , 100%). Found: C, 66.31; H, 6.36; N, 3.80. Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_3\cdot\text{HCl}$: C, 66.38; H, 6.69; N, 3.87%.

DESCRIPTION 18: (2R*,3R*)-3-((3-Carboxamidophenyl)methyloxy)-2-phenylpiperidine

The second compound to elute from the column described in 17b above was isolated as a colourless oil. ^1H NMR (360MHz, CDCl_3) δ 1.2-2.2 (4H, m), 2.82 (1H, mc), 3.27 (1H, mc), 3.66 (1H, s), 3.82 (1H, s), 4.16 (1H, d, $J = 12\text{Hz}$, OCHH), 4.48 (1H, d, $J = 12\text{Hz}$, OCHH), 5.53 (1H, brs, CONHH), 6.18 (1H, brs, CONHH), 7.0-7.4 (9H, m, ArH).

- 45 -

DESCRIPTION 19: (2R*.3R*)-3-((2-Methoxy-3-nitrophenyl)methyloxy)-2-phenylpiperidinium hydrochloride

5 This compound was prepared from the compound of Description 1c and 2-methoxy-5-nitrobenzyl bromide, following the procedure described in Descriptions 1c-e. mp 246-248°C. MS (CI⁺) m/z 343 (M⁺+1, 45%). Found: C, 60.52; H, 5.96; N, 7.45. Calcd. for C₁₉H₂₂N₂O₄.HCl: C, 60.24; H, 6.12; N, 7.39%.

10 DESCRIPTION 20: (2R*.3R*)-3-((5-Amino-2-methoxyphenyl)methyloxy)-2-phenylpiperidinium hydrochloride

The compound of Description 19 (0.342g) was dissolved in methanol (20ml) with hydrochloric acid (1ml, 2N). Palladium on charcoal (50mg) was added and the mixture placed under an atmosphere of hydrogen for 1h at room temperature. The solvent was removed *in vacuo* and the residue basified with sodium hydroxide (2M). This solution was extracted with ethyl acetate and the organic extracts were dried (MgSO₄) and concentrated to leave a brown oil; this was purified by column chromatography on silica using 8% methanol in dichloromethane as eluent. The resulting oil was characterised as the salt prepared by treatment with methanolic hydrogen chloride: mp 241-243°C.

25 The following piperidines were prepared according to the procedures outlined in Descriptions 1 and 3, using the appropriate benzyl halide.

30 DESCRIPTION 21: (2S,3S)-2-Phenyl-3-((3-(trifluoromethyl)phenyl)methyloxy)piperidine

- 46 -

¹H NMR (CDCl₃) δ 1.4-2.2 (4H, m), 2.45 (1H, brs), 2.83 (1H, td, J=13Hz and 4Hz), 3.3 (1H, m), 3.64 (1H, d, J=2Hz), 3.82 (1H, d, J=2Hz), 4.13 (1H, d, J=12Hz, OCHH), 4.42 (2H, J=12Hz, OCHH), 7.75 (m, 9H, ArH).

5

DESCRIPTION 22: (2S,3S)-3-((3,4-Dichlorophenyl)methoxy)-2-phenylpiperidinium hydrochloride

¹H NMR (DMSO-d₆) 1.65-1.8 (2H, m), 1.8 (1H, m), 2.16 (1H, d, J=12Hz), 3.05 (1H, m), 3.25 (1H, m), 3.83 (1H, s), 4.12 (1H, d, J=12Hz), 4.5 (2H, m), 7.05 (1H, dd, J=7 & 2Hz), 7.28 (1H, d, J=2Hz), 7.35-7.5 (6H, m), 9.05 (1H, br s), 9.8 (1H, br s).

10

DESCRIPTION 23: (2S,3S)-3-((2,3-Dimethylphenyl)methoxy)-2-phenylpiperidinium hydrochloride

Ethyl acetate (10ml) was saturated with hydrogen chloride by passing HCl gas for 5 min and a solution of 0.254g of (2S,3S)-1-*t*-butoxycarbonyl-3-((2,3-dimethylphenyl)methoxy)-2-phenylpiperidine (prepared according to Description 3d) in 7ml of ethyl acetate was added. After stirring for 2h, the reaction mixture was concentrated *in vacuo*. The residual white solid was washed with ether, filtered and dried to obtain 0.23g of (2S,3S)-3-((2,3-dimethylphenyl)methoxy)-2-phenylpiperidinium hydrochloride. ¹H NMR (DMSO-d₆) δ 1.6-1.9 (3H, m), 1.75 (3H, s), 2.15 (3H, s), 2.2 (1H, m), 3.05 (1H, m), 3.25 (1H, m), 3.84 (1H, s), 4.05 (1H, d, J=14Hz), 4.45 (1H, d, J=14Hz), 4.48 (1H, s), 6.95-7.5 (8H, m), 8.8 (1H, br s), 9.4 (1H, br s).

15

20

25

30

DESCRIPTION 24: (2S,3S)-3-((3-*t*-Butylphenyl)methoxy)-2-phenylpiperidinium hydrochloride

- 47 -

¹H NMR (360MHz, CDCl₃) δ 1.21 (9H, s, C(CH₃)₃), 1.45 (3H, s), 1.52-1.67 (2H, m, CH₂), 2.04-2.12 (1H, m, CHH), 2.30-2.34 (1H, m, CHH), 2.93-2.96 (1H, m, NCHH), 3.54 (1H, d, J=13Hz, NCHH), 3.72 (1H, s, NCHCHO), 4.14 (1H, d, J=2Hz, NCHCHO), 4.28-4.36 (2H, q, J=13Hz, OCHH), 6.87-6.89 (1H, m, ArH), 7.05 (1H, s, ArH), 7.11-7.15 (1H, m, ArH), 7.20-7.34 (4H, m, ArH), 7.55-7.58 (2H, m, ArH). MS (CI+) m/z 323 (M⁺+1, 100%).

10 DESCRIPTION 25: (2R*,3R*)-3-((3,5-Dimethylphenyl)methoxy)-2-phenylpiperidinium hydrochloride

¹H NMR (360MHz, CDCl₃) δ 1.48 (m), 1.62 (m), 1.86 (m), 2.20 (s), 2.82 (ddd, J=3.0, 3.0, 12.6Hz), 3.26 (dt, J=2.15, 2.15, 12.5Hz), 3.63 (s), 3.78 (s), 4.10 (d, J=12.0Hz), 4.33 (d, J=12.0Hz), 6.31 (s), 7.2-7.4 (m). MS (CI+) m/z 296 (M⁺+1).

DESCRIPTION 26: (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-(3-chlorophenyl)piperidine

20 (a) Methyl-4-nitrobutyrate and 3-chlorobenzaldehyde were reacted in an analogous manner to that described in Description 1a to give 2-(3-chlorophenyl)-3-nitro-6-oxopiperidine: mp 131-133°C. ¹H NMR (360MHz, CDCl₃) δ 2.26-2.36 (1H, m), 2.50-2.72 (3H, m), 4.66-4.71 (1H, m), 5.24-5.28 (1H, d), 6.57 (1H, s), 7.17-7.40 (4H, m).

25 (b) The product of part a) was treated analogously to that described in Description 1b to give 2-(3-chlorophenyl)-3,6-dioxo piperidine: mp 144-147°C. ¹H NMR (360MHz, CDCl₃) δ 2.8 (4H, m), 5.0 (1H, d), 6.4 (1H, s), 7.22-7.42 (4H, m).

- 48 -

c) The product of part b) was treated analogously to that described in Description 1c and 3a to give cis-2-(3-chlorophenyl)-3-hydroxypiperidine tosylate salt: mp > 250°C. ¹H NMR (360MHz, CDCl₃) δ 1.60-2.07 (4H, m), 2.28 (3H, s), 3.00-3.11 (1H, m), 4.02 (1H, s), 4.62-4.66 (1H, d), 5.96 (1H, s), 7.10-7.20 (2H, d), 7.41-7.59 (6H, m).

d) The product of part c) was treated analogously to that described in Description 1c to give cis-1-t-butyloxycarbonyl-2-(3-chlorophenyl)-3-hydroxypiperidine as a clear, viscous oil. ¹H NMR (360MHz, CDCl₃) δ 1.40 (9H, s), 1.61-1.90 (4H, m), 2.88-3.01 (1H, ddd), 3.93-3.99 (1H, dd), 4.03-4.10 (1H, m), 5.33 (1H, d), 7.20-7.26 (2H, m), 7.34-7.38 (1H, m), 7.47-7.52 (1H, m). m/z (CI-) 310, 312; m/z (CI+) 312, 314.

e) The product of part d) and 3,5-bis(trifluoromethyl)benzylbromide were treated in an analogous manner to that described in Description 1d to give cis-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-1-t-butyloxy-carbonyl-2-(3-chlorophenyl)piperidine. ¹H NMR (250MHz, CDCl₃) δ 1.24-1.30 (1H, m), 1.47 (9H, s), 1.60-2.00 (3H, m), 2.67-2.80 (1H, ddd), 3.81-4.01 (2H, m), 4.8 (2H, s), 5.61-5.67 (1H, d), 7.23-7.27 (2H, m), 7.39-7.44 (1H, m), 7.6 (1H, s), 7.78 (2H, s), 7.8 (1H, s).

f) The product of part e) was treated in an analogous manner to that described in Description 1e to give cis-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-(3-chlorophenyl)piperidine hydrochloride salt, mp = 158°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.70-1.96 (4H, m), 2.19-2.28 (1H, m), 3.02-3.13 (1H, m), 3.84 (1H, s), 4.35-4.39 (2H, d), 4.60 (1H, s), 4.79-4.85 (2H, d), 7.39-7.44 (3H, m), 7.58 (1H, s), 7.84 (2H, s), 7.97 (1H, s), 9.2 (br s), 10.05 (br s). Found: C, 50.44; H, 4.13; N, 3.01. C₂₀H₁₈ClF₆NO.HCl requires C, 50.65; H, 4.04; N, 2.95%. m/z (CI+), 438, 440.

- 49 -

DESCRIPTION 27: 2S,3S)-3-((3-Fluoro-5-methylphenyl)methoxy)-2-phenylpiperidine

mp 219-221°C. ¹H NMR (360MHz, CDCl₃) δ 1.50-1.68 (2H, m), 2.11-2.15 (1H, m), 2.20 (3H, s, CH₃), 2.31-2.35 (1H, m), 2.94-2.98 (1H, m, NCHH), 3.55-3.58 (1H, d, J = 12Hz, NCHH), 3.69 (1H, bs, CHO), 4.15-4.18 (1H, m, CHPh), 4.18 (1H, d, J = 13Hz, OCHH), 4.33 (1H, d, J = 13Hz, OCHH), 6.47 (1H, d, ArH), 6.59 (1H, s, ArH), 6.66 (1H, d, ArH), 7.26-7.37 (3H, m, ArH), 7.52-7.54 (2H, m, ArH). MS (CI⁺) m/z 300 (M⁺+1, 100%).

DESCRIPTION 28: (3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-methyl-2-(2R*)-2-phenylpiperidine

(a) 3,6-Dioxo-2-phenylpiperidine (Description 1b) (5g) was dissolved in dimethylformamide (25ml) at 0°C. Sodium hydride (873mg, 80% dispersion in oil) was added portionwise and the mixture stirred for 15 min. Methyl iodide was added (1.8ml) and the mixture was stirred for 12h. The mixture was diluted with water (250ml) and extracted with ethyl acetate (3 x). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated to leave a solid: 3,6-dioxo-2-methyl-2-phenylpiperidine.

(b) The ketone of (a) above (3.2g) was suspended in methanol under nitrogen and the temperature brought to -40°C. Sodium borohydride (0.3g) was added portionwise. The mixture was stirred for 30 min and then concentrated *in vacuo*, azeotroping with tetrahydrofuran. Borane tetrahydrofuran complex (64ml, 1.0M in tetrahydrofuran) was added and the mixture was heated at reflux overnight. The mixture was cooled and quenched carefully with methanol, and the mixture was

- 50 -

then concentrated *in vacuo*. The resulting residue was dissolved in ethanol (100ml) and potassium carbonate (4.2g) was added. The mixture was heated at reflux for 12h. The mixture was cooled and evaporated and the residue was extracted with ethyl acetate and water. The organic extract was washed with brine, dried (MgSO₄) and evaporated to afford 3-hydroxy-2-methyl-2-phenylpiperidine as a white solid. ¹H NMR (360MHz, CDCl₃) δ 7.79 (2H, d, ArH), 7.40 (2H, t, ArH), 7.15-7.19 (1H, m, ArH), 3.89 (1H, mc), 2.89-3.01 (2H, m), 1.67-1.91 (4H, m), 1.39 (3H, s, CH₃).

(c) The alcohol of (b) above (3g) was dissolved in dichloromethane (50ml) and di-*t*-butyldicarbonate (3.48g) was added. The solution was allowed to stir for 12h. The solution was concentrated *in vacuo* and the residue was purified by chromatography on silica using ethyl acetate in petrol (20:80) as eluent. This afforded N-*t*-butyloxycarbonyl-2-hydroxy-2-methyl-2-phenylpiperidine as a clear oil. ¹H NMR (250MHz, CDCl₃) δ 1.08 (9H, s, (CH₃)₃), 1.80 (3H, s, CH₃), 1.6-2.0 (4H, m), 3.6-3.74 (2H, m), 3.8-3.92 (1H, m, CHO), 7.2-7.36 (5H, m, ArH).

(d) The alcohol of (c) above (2.2g) was dissolved in dry dimethylformamide (12ml). Sodium hydride was added (0.36g, 60% dispersion in oil) portionwise and the mixture was allowed to stir at room temperature for 30 min. 3,5-Bis(trifluoromethyl)benzyl bromide (3.5g) was added dropwise and the mixture was allowed to stir for 5h. The mixture was diluted with aqueous ammonium chloride, extracted with ethyl acetate and the organic extract was washed with brine, dried (MgSO₄) and evaporated *in vacuo*. The residue as purified by column chromatography on silica using a gradient elution, 100% petrol to 10% ethyl acetate in petrol as eluant, to afford the product 3-((3,5-bis(trifluoromethyl)phenyl)methoxy-1-*t*-

- 51 -

butyloxycarbonyl-2-methyl-2-phenylpiperidine as a colourless oil. ^1H NMR (360MHz, CDCl_3) δ 1.13 (9H, s, $(\text{CH}_3)_3$), 1.85 (3H, s, CH_3), 1.85-1.99 (4H, m, CH_2CH_2), 3.48 (1H, brs, NCHH), 3.68-3.75 (1H, m, NCHH), 3.80-3.85 (1H, m, CHO), 3.85 (1H, d, $J = 12\text{Hz}$, OCHH), 4.36 (1H, d, $J = 12\text{Hz}$, OCHH), 7.17-7.32 (5H, m, ArH), 7.42 (2H, s, ArH), 7.71 (1H, s, ArH).

(e) The compound of (d) above (2.1g) was dissolved in trifluoroacetic acid (30ml) for 10 min and was then evaporated *in vacuo*. The residue was dissolved in dichloromethane, washed with sodium hydroxide (2M), water and brine, then dried (MgSO_4) and concentrated *in vacuo*. Methanolic hydrogen chloride was added to the residue and when dissolved the solvent was evaporated. The residue was triturated with ether to afford the product as a white powder: (3R*)-3-((3,5-Bis(trifluoromethyl) phenyl)methoxy)-2-methyl-(2R*)-2-phenylpiperidine. ^1H NMR (360MHz, DMSO) δ 1.67 (3H, s, CH_3), 1.70 (1H, m), 1.84-1.91 (1H, m), 1.99-2.06 (2H, m), 3.16 (1H, m), 3.33 (1H, m), 4.19 (1H, s), 4.29 (1H, d, $J=12\text{Hz}$, OCHH), 4.75 (1H, d, $J=12\text{Hz}$, OCHH), 7.29-7.33 (1H, m, ArH), 7.37-7.41 (3H, m, ArH), 7.54 (2H, s, ArH), 7.56 (1H, brs, ArH), 7.89 (1H, s, ArH). Found: C, 55.38; H, 4.92; N, 3.08 Calcd. for $\text{C}_{21}\text{H}_{21}\text{F}_6\text{NO}$: C, 55.58; H, 4.89; N, 3.09%.

DESCRIPTION 29: (2S,3S)-3-((3,4-Dimethylphenyl) methoxy)-2-phenylpiperidine

^1H NMR (CDCl_3) δ 1.4-1.9 (3H, m), 2.11 (3H, s), 2.17 (3H, s), 2.1-2.3 (1H, m), 2.78 (1H, m), 3.25 (1H, m), 3.60 (1H, s), 3.76 (1H, s), 4.08 (1H, d, $J=12\text{Hz}$), 4.27 (1H, d, $J=12\text{Hz}$), 6.7 (2H, m), 6.92 (1H, d, $J=9\text{Hz}$), 7.2-7.5 (5H, m).

- 52 -

DESCRIPTION 30: (2S,3S)-3-((3-(*iso*Propoxy)phenyl)methyloxy)-2-phenylpiperidine

¹H NMR (250MHz, CDCl₃) δ 1.6-1.9 (3H, m), 1.97 (1H, d, J=7Hz), 2.16 (1H, m), 3.05 (1H, m), 3.3 (1H, m), 3.84 (1H, s), 4.09 (1H, d, J=12Hz), 4.41 (1H, d, J=12Hz), 4.44 (1H, m), 4.5 (1H, s), 6.6 (2H, m), 6.72 (1H, m), 7.09 (1H, t, J=8Hz), 7.3-7.5 (5H, m).

DESCRIPTION 31: (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-(3-fluorophenyl)piperidine

¹H NMR (360MHz, CDCl₃) δ 1.66-1.9 (3H, m), 2.2-2.3 (1H, m), 2.43-2.5 (1H, m), 3.0-3.2 (1H, m), 3.98 (1H, s), 4.37 (1H, d, J=12Hz), 4.62 (1H, s), 4.79 (1H, d, J=12Hz), 7.04-7.46 (4H, m, ArH), 7.80 (2H, s, ArH), 7.96 (1H, s, ArH).

EXAMPLE 1

3-Amino-5-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidinolmethyl]-1,2,4-oxadiazole

Hydroxyguanidine sulphate hydrate (2.3g) was dissolved in water and freeze-dried overnight. Ethanol (35ml) and powdered molecular sieves (1g) were added to the solid hydroxyguanidine and the suspension was stirred under nitrogen for 1 hour. Sodium (670mg) was added to the mixture which was stirred until all sodium had reacted. The suspension assumed an orange colour at this time and was placed in an ultrasound bath for 15 min. The ester of Description 2 (1.4g) was added to the mixture which was then heated at reflux for 2h. The reaction mixture was cooled and filtered through celite.

- 53 -

Ethanol was removed *in vacuo* and the residue was extracted into ethyl acetate and washed with water and brine. The organic layer was dried (MgSO₄) and evaporated. The residue was purified on silica using 25% ethyl acetate in petrol as eluant. This afforded the product (800mg) as a solid which was recrystallised from ether/hexane to afford colourless prisms: mp 160-161°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.47-1.54 (2H, m, CH₂), 1.85-1.9 (1H, m, CHH), 2.14-2.17 (1H, m, CHH), 2.35-2.40 (1H, m, CHHN), 2.99-3.02 (1H, m, CHHN), 3.35 (1H, d, J = 15.0Hz, N-CHH-oxadiazole), 3.60 (2H, brs, NCHCHO), 3.65 (1H, d, J = 15.0Hz, N-CHH-oxadiazole), 4.06 (1H, d, J = 13.0Hz, OCHH), 4.62 (1H, d, J = 13.0Hz, OCHH), 6.2 (2H, brs, NH₂), 7.23-7.31 (3H, m, ArH), 7.42-7.44 (2H, m, ArH), 7.69 (2H, s, ArH), 7.93 (1H, s, ArH); MS (CI⁺) m/z 501 ((M+1)⁺, 75%). Found: C, 54.81; H, 4.47; N, 11.2. Calcd. for C₂₃H₂₂F₆N₄O₂: C, 55.20; H, 4.43; N, 11.2%.

EXAMPLE 2

5-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinomethyl]-3-methyl-1,2,4-oxadiazole

Acetamideoxime (117mg) and powdered molecular sieves were suspended in dry tetrahydrofuran (10ml) and stirred under nitrogen for 1 hour. Sodium hydride (63mg of 60% suspension in oil) was added and the mixture heated to 50°C until all hydrogen evolution had ceased. The ester of Description 2 (500mg) was dissolved in tetrahydrofuran (2ml) and added to the above mixture. This mixture was heated at reflux for 2h, cooled, filtered through celite and evaporated *in*

- 54 -

vacuo. The residue was dissolved in ethyl acetate and washed with water and then brine. The organic layer was dried (MgSO_4) and evaporated *in vacuo*. The residue was purified by medium pressure chromatography (Lobar) using 25% ethyl acetate in petrol as eluant. This afforded the product as a crystalline solid: mp 85-86°C; ^1H NMR (360MHz, DMSO-d_6) δ 1.47-1.54 (2H, m, CH_2), 1.85-1.89 (1H, m, CHH), 2.13-2.17 (1H, m, CHH), 2.31 (3H, s, CH_3), 2.34-2.40 (1H, m, CHHN), 2.98-3.01 (1H, m, CHHN), 3.51 (1H, d, $J = 15.0\text{Hz}$, NCHH-oxadiazole), 3.60 (2H, s, NCHCHO), 3.81 (1H, d, $J = 15.0\text{Hz}$, NCHH-oxadiazole), 4.06 (1H, d, $J = 13.0\text{Hz}$, OCHH), 4.62 (1H, d, $J = 13.0\text{Hz}$, OCHH), 7.25-7.31 (3H, m, ArH), 7.43-7.45 (2H, m, ArH), 7.70 (2H, s, ArH), 7.93 (1H, s, ArH); MS (EI) m/z 500 ($(\text{M}+1)^+$, 100%). Found: C, 57.94; H, 4.79; N, 8.23. Calcd. for $\text{C}_{24}\text{H}_{23}\text{F}_6\text{N}_3\text{O}_2$: C, 57.72; H, 4.64; N, 8.41%.

EXAMPLE 3

(+)- 3-Amino-5-[(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidinolmethyl]-1,2,4-oxadiazole

The title compound was prepared from the ester of Description 4 using the procedure described in Example 1: mp 138-139°C; $[\alpha]_{\text{D}}^{23} = +147.7^\circ$ ($c=1$, MeOH). ^1H NMR (360MHz, CDCl_3) δ 1.47-1.50 (2H, m, CH_2), 1.85-1.89 (1H, m, CHH), 2.14-2.17 (1H, m, CHH), 2.35-2.41 (1H, m, CHHN), 2.99-3.02 (1H, m, CHHN), 3.29 (1H, s, NCHCHO), 3.33 (1H, d, $J = 15.0\text{Hz}$, NCHH-het), 3.65 (1H, d, $J = 15.0\text{Hz}$, NCHH-het), 3.60 (1H, brs, NCHPh), 4.05 (1H, d, $J = 13.0\text{Hz}$, OCHH), 4.62 (1H, d, $J = 13.0\text{Hz}$, OCHH), 6.20 (2H, s, NH_2), 7.23-7.31 (3H, m, ArH), 7.42-7.44 (2H, m, ArH), 7.69 (2H, s, ArH), 7.93 (1H, s, ArH); MS

- 55 -

(Cl^+) m/z 501 ($M+1^+$, 75%). Found: C, 54.81; H, 4.47; N, 11.2.
Calcd. for $\text{C}_{23}\text{H}_{22}\text{F}_6\text{N}_4\text{O}_2$: C, 54.98; H, 4.54; N, 11.30%.

EXAMPLE 4

5 3-[[[(2R*,3R*)-3-[(3,5-Bis(trifluoromethyl)phenyl)
methoxy]-2-phenylpiperidinol)methyl]pyridinium
hydrochloride

10 The compound of Description 1 (410mg), 3-picolyl chloride (167mg) and potassium carbonate were suspended in dimethylformamide (3ml) and the mixture heated at 60°C for 12h. The mixture was cooled, diluted with water (50ml) and extracted with ethyl acetate (2 x 10ml). The organic phase was washed with brine, dried (MgSO_4) and evaporated. The residue was purified on silica using a gradient elution of 25-50% ethyl acetate in petrol. The product was dissolved in ethereal hydrogen chloride to form the dihydrochloride salt which was recrystallised from benzene: mp 198-200°C. ^1H NMR (360MHz, $\text{DMSO}-d_6$, 353K) δ 1.68-1.82 (2H, m, CH_2), 2.09-2.18 (2H, m, CH_2), 3.06 (1H, mc, CHHN), 3.37 (1H, mc, CHHN), 3.89 (1H, s, NCHCHO), 4.16 (1H, brd, NCHH-pyridine), 4.20 (1H, brd, NCHH-pyridine), 4.26 (1H, d, $J = 13.0\text{Hz}$, CHHO), 4.56 (1H, brs, NCHPh), 4.72 (1H, d, $J = 13.0\text{Hz}$, CHHO), 7.37-7.41 (3H, m, ArH), 7.60-7.64 (1H, m, ArH), 7.71-7.72 (2H, m, ArH), 7.86 (1H, s, ArH), 7.89 (2H, s, ArH), 8.08 (1H, d, $J = 8.0\text{Hz}$, ArH), 8.64 (1H, s, ArH), 8.68 (1H, d, $J = 5.0\text{Hz}$, ArH); MS (Cl^+) m/z 495 (M^++1 , 60%); Found: C, 52.45; H, 4.90; N, 4.52. Calcd. for $\text{C}_{26}\text{H}_{24}\text{F}_6\text{N}_2\text{O} \cdot 2\text{HCl} \cdot 1.5\text{H}_2\text{O}$: C, 52.54; H, 4.92; N, 4.71%.

25

30

- 56 -

EXAMPLE 5

2-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]pyridinium hydrochloride

5 The compound of Description 1 was reacted with 2-picoyl chloride following the procedure illustrated in Example 4: mp 175-180°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.65-1.83 (2H, m, CH₂), 2.08-2.15 (2H, m, CH₂), 3.16-3.20 (1H, m, CHHN), 3.30-3.40 (1H, m, CHHN), 3.70 (1H, s, NCHCHO), 4.18 (1H, d, J = 14.0Hz, CHH-pyridine), 4.23 (1H, d, J = 14.0Hz, CHH-pyridine), 4.30 (1H, d, J = 13.0Hz, OCHH), 4.79 (1H, d, J = 13.0Hz, OCHH), 4.78 (1H, s, CHPh), 7.24 (1H, d, J = 7.5Hz, ArH), 7.36-7.4 (3H, m, ArH), 7.47-7.51 (1H, m, ArH), 7.62 (2H, mc, ArH), 7.85 (1H, dt, J = 7.5, 2.0Hz, ArH), 7.94 (2H, s, ArH), 7.97 (1H, s, ArH), 8.65 (1H, d, J = 7.5Hz, ArH); MS (Cl⁺) m/z 495 (M+1)⁺, 100%). Found: C, 53.01; H, 4.79; N, 4.69. Calcd. for C₂₆H₂₄F₆N₂O.2HCl.H₂O : C, 53.30; H, 4.82; N, 4.78%.

10

15

EXAMPLE 6

2-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]benzimidazole

20 The compound of Description 1 was reacted with 2-(chloromethyl)benzimidazole following the procedure illustrated in Example 4: mp 152-153°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.44-1.59 (2H, m, NCH₂CH₂CH₂), 1.85-1.89 (1H, m, CHHCH₂N), 2.15-2.18 (2H, m, NCHH+CHHCH₂N), 2.86-2.89 (1H, m, NCHH), 3.15-3.19 (1H, d, J = 14.0Hz,

25

- 57 -

NCHH-imidazole), 3.57 (1H, s, NCHCHO), 3.63 (1H, s, NCHCHO), 3.80-3.84 (1H, d, J = 14.0Hz, NCHH-imidazole), 4.10-4.13 (1H, d, J = 13.0Hz, -OCHH), 4.63-4.66 (1H, d, J = 13.0Hz, -OCHH), 7.07-7.15 (2H, m, ArH), 7.24-7.34 (3H, m, ArH), 7.43-7.52 (2H, m, ArH), 7.60-7.62 (2H, m, ArH), 7.67 (2H, s, ArH), 7.94 (1H, s, ArH), 12.10 (1H, s, NH); MS (CI⁺) m/z 534 ((M+1)⁺, 100%).

EXAMPLE 7

10 5-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl]tetrazole

The compound of Description 5 (1.0g), triethylamine hydrochloride (467mg) and sodium azide (441mg) were dissolved in 1-methyl-2-pyrrolidinone (5ml) and the reaction mixture was heated at reflux under nitrogen for 2h. The mixture was then cooled, and diluted with ice/water (80ml) and acidified to pH = 2 with methanolic hydrogen chloride. This precipitated the product as a white solid, which was purified on silica using a gradient elution of methanol in dichloromethane (0-5%). The product was recrystallised from ether-hexane: mp 114-115°C.

15 ¹H NMR (360MHz, DMSO-d₆) δ 1.59-1.65 (2H, m, NCH₂CH₂CH₂), 2.02-2.22 (2H, m, NCH₂CH₂), 2.39-2.46 (1H, m, CHHN), 2.98-3.02 (1H, m, CHHN), 3.62 (1H, s, NCHCHO), 3.66 (1H, s, NCHCHO), 3.70-3.74 (1H, d, J = 15.5Hz, NCHH-tetrazole), 4.05-4.10 (1H, d, J = 15.5Hz, NCHH-tetrazole), 4.08-4.12 (1H, d, J = 12.0Hz, OCHH), 4.51-4.54 (1H, d, J = 12.0Hz, OCHH), 5.30 (1H, s, NH), 7.30-7.35 (3H, m, ArH), 7.45-7.47 (2H, m, ArH), 7.51 (2H, s, ArH), 7.74 (1H, s, ArH); MS (CI⁺) m/z 486 (M⁺+1, 85%). Found: C, 53.14;

- 58 -

H, 4.58; N, 13.96. Calcd. for $C_{22}H_{21}F_6N_5O \cdot 0.5H_2O$: C, 53.44; H, 4.48; N, 14.16%.

EXAMPLE 8

5 2-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)
 methyloxy)-2-phenylpiperidinolmethyl]-4-methyl-1,3-thiazole

 Anhydrous acetone (2ml) and methanol (2ml) and
 tetrabutylammonium perbromide (111mg) were stirred under
 nitrogen to generate a solution of bromoacetone *in situ*. The
10 compound of Description 6 (150mg) was added to this mixture
 and the resulting solution was stirred for 2h. A second
 equivalent of bromoacetone was added and the mixture was
 stirred for a further 2h. The volatile solvents were removed *in*
 vacuo and the residue was dispersed between aqueous
15 potassium carbonate and ethyl acetate. The organic phase was
 washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*
 affording a brown oil. This was purified on silica using a
 gradient elution of ethyl acetate in petrol (10-30%) which gave
 the product as a clear oil: 1H NMR (360MHz, $CDCl_3$) 1.51-1.68
20 (2H, m, CH_2), 1.98-2.22 (2H, m, CH_2), 2.26-2.37 (1H, m, $NCHH$),
 2.38 (3H, s, CH_3), 3.18-3.26 (1H, m, $NCHH$), 3.47 (1H, d, J =
 15.0Hz, $NCHH$), 3.54 (H, bs, CHO), 3.58 (H, bs, $CHPh$), 3.94
 (1H, d, J = 15.0Hz, $NCHH$), 4.01 (1H, d, J = 12.5Hz, $OCHH$),
 4.47 (1H, d, J = 12.5Hz, $OCHH$), 6.80 (1H, s, SCH), 7.24-7.35
25 (3H, m, Ar-H), 7.52-7.54 (2H, m, Ar-H), 7.58 (2H, s, Ar-H), 7.72
 (1H, s, Ar-H); MS (CI^+) m/z 515 ($M^+ + 1$, 100%). Found: C, 58.59;
 H, 4.88; N, 5.48 Calc for $C_{25}H_{24}F_6N_2OS$: C, 58.36; H, 4.70; N,
 5.44%.

- 59 -

EXAMPLE 9(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(2-furoyl)-2-phenylpiperidine

The compound of Description 1 (400mg) and triethylamine (300mg) were dissolved in dichloromethane and the mixture was stirred for 10 min at 0°C. 2-Furoyl chloride (155mg) was added to the solution and the reaction mixture was stirred for 15 min. The mixture was then washed with brine; the organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by chromatography on silica using 20% ethyl acetate in petrol, affording a clear oil. ¹H NMR (360MHz, DMSO-d₆) δ 1.6-1.8 (2H, m, CH₂), 1.9-2.1 (2H, m, CH₂), 2.99 (1H, mc, CHHN), 4.02 (1H, q, J = 5.0Hz, CHO), 4.0-4.2 (1H, m, CHHN), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.86 (1H, d, J = 13.0Hz, OCHH), 5.95 (1H, s, CHPh), 6.62 (1H, s, furan-H), 6.99 (1H, s, furan-H), 7.25-7.36 (3H, m, ArH), 7.51-7.54 (2H, m, ArH), 7.83 (1H, s, furan-H), 7.90 (2H, s, ArH), 7.99 (1H, s, ArH); MS (CI⁺) m/z 498 (M⁺+1, 20%).

20

EXAMPLE 102-(((2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl)furan

The compound of Example 9 (340mg) was dissolved in tetrahydrofuran. To this solution was added borane-dimethyl sulfide complex (0.18ml of 10M solution) and the resulting solution was heated at reflux for 8h. The mixture was cooled, methanol added to quench excess borane, and the solvents were removed *in vacuo*. The residue was dissolved in methanol

25

- 60 -

(10ml) and potassium carbonate was added (238mg). This mixture was heated at reflux for 1 hour; the methanol was removed *in vacuo* and the residue was dispersed between ethyl acetate and brine. The ethyl acetate layer was dried (MgSO_4) and evaporated. The residue was purified by chromatography on silica using 10% ethyl acetate in petrol. The product was recrystallised from ether-hexane: mp 103-104°C. ^1H NMR d 1.4-1.5 (2H, m, CH_2CH_2), 1.8-1.9 (1H, m, CHHCH_2N), 2.1-2.2 (2H, m, CHHCH_2N and CHHN), 2.95-3.0 (1H, m, CHHN), 3.11-3.15 (1H, d, $J = 15.0\text{Hz}$, NCHH-furan), 3.38 (1H, s, NCHCHO), 3.54-3.58 (1H, d, $J = 15.0\text{Hz}$, NCHH-furan), 3.56 (1H, s, NCHCHO), 4.02-4.06 (1H, d, $J = 13.0\text{Hz}$, OCHH-), 4.59-4.62 (1H, d, $J = 13.0\text{Hz}$, OCHH-), 6.08-6.09 (1H, m, furan H), 6.35-6.36 (1H, m, furan-H), 7.24-7.32 (3H, m, ArH), 7.46-7.48 (2H, m, ArH), 7.55 (1H, s, furan-H), 7.68 (2H, s, ArH), 7.93 (1H, s, ArH); MS (Cl^+) m/z 485 (M^++1 , 100%). Found: C, 62.11; H, 4.80; N, 2.90. Calcd. for $\text{C}_{25}\text{H}_{23}\text{NF}_6\text{O}$: C, 62.27; H, 4.83; N, 2.96.

EXAMPLE 11

5-[[[(2R*,3R*)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinol)methyl]-3-bromo-1,2,4-oxadiazole hydrochloride

Diisopropylethylamine (220 μl) was added to a stirred suspension of the compound of Description 1 (200mg) and 5-bromo-3-(chloromethyl)-1,2,4-oxadiazole (99mg) (J. Heterocyclic Chem. 1989, 26, 23) in dry acetonitrile. The resulting solution was allowed to stir at room temperature for 48 hrs. After this time the solvent was removed under reduced pressure and the residual oil purified by column

- 61 -

chromatography on silica using ethyl acetate in hexane (20%) as eluant to afford a waxy solid. Treatment of an ethereal solution of this solid with ethereal hydrogen chloride yielded a white precipitate. Recrystallisation from ether afforded the title compound as an amorphous white solid: mp 100-102°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.67-1.70 (2H, m, CH₂), 1.83 (1H, m, CHH), 2.30 (1H, m, CHH), 2.74 (1H, m, CHHN), 3.10 (1H, m, CHHN), 3.70 (1H, d, J = 11.0Hz, CH-OCH₂), 3.82 (1H, brs, N-CH-Ph), 4.34 (1H, d, J = 16.0Hz, NCHH-oxadiazole), 4.36 (1H, d, J = 11.0Hz, OCHH-Ar), 4.58 (1H, d, J = 16.0Hz, NCHH-oxadiazole), 4.73 (1H, d, J = 11.0Hz, OCHH-Ar), 7.34-7.42 (5H, m, ArH), 7.68 (2H, s, ArH), 7.73 (1H, s, ArH); MS (Cl⁺) m/z 564 ((M+1)⁺, 20%). Found: C, 45.64; H, 3.63; N, 6.70. Calcd. for C₂₃H₂₀N₃O₂F₆Br.HCl: C, 45.98; H, 3.52; N, 6.99%.

EXAMPLE 12

5-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinomethyl]-3-dimethylamino-1,2,4-oxadiazole hydrochloride

The compound of Example 11 (169mg) in dimethylamine (33% in ethanol) was heated to 40°C for 30 min. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica using ethyl acetate in hexane (20%) as eluant. The compound was dissolved in ether and treated with excess ethereal hydrogen chloride to afford a white precipitate. Recrystallisation from ether afforded the product as white powder (110mg): mp 179-180°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.59 (2H, m, CH₂), 2.1-2.21 (2H, m, CH₂), 2.4-2.45 (1H, m, CHHN), 3.01 (6H, s, N(CH₃)₂), 3.10 (1H, m,

- 62 -

CHHN), 3.60 (1H, brs, CH-O-CH₂), 3.70 (1H, d, J = 16.0Hz, NCHH-oxadiazole), 3.78 (1H, d, J = 1.0Hz, N-CH-Ph), 3.82 (1H, d, J = 16.0Hz, NCHH-oxadiazole), 4.01 (1H, d, J = 15.0Hz, O-CHH-Ar), 4.49 (1H, d, J = 15.0Hz, O-CHH-Ar), 7.3 (3H, m, ArH), 7.4 (2H, m, ArH), 7.49 (2H, s, ArH), 7.64 (1H, s, ArH); MS (Cl⁺) m/z (M⁺+1) 529. Found: C, 51.87; H, 4.93; N, 9.62. Calcd. for C₂₅H₂₆N₄O₂F₆·HCl·H₂O. C, 51.51; H, 5.01; N, 9.61%.

EXAMPLE 13

10 (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(2-thienovl)piperidine

The compound of Description 1 was reacted with 2-thiophenecarbonyl chloride as outlined in Example 9. The oil obtained after work-up and removal of solvent was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether to afford the pure product as a clear oil. ¹H NMR (250MHz, CDCl₃) d 1.6-1.8 (2H, m, CH₂), 2.1-2.2 (2H, m, CH₂), 3.0 (1H, m, CHN), 4.0 (1H, dt, J = 5Hz, 2Hz, CH), 4.1 (1H, brs, CHN), 4.7 (1H, d, J = 7Hz, CHAr), 4.8 (1H, d, J = 7Hz, CHAr), 6.2 (1H, brs, NCHPh), 7.02 (1H, dd, J = 1, 2Hz, thiophene-H), 7.3-7.44 (4H, m, Ar-H), 7.5 (1H, dd, J = 1, 3Hz, thiophene-H), 7.6-7.92 (5H, m, Ar-H).

EXAMPLE 14

25 (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(2-thienylmethyl)piperidine

The compound of Example 13 was reacted with borane dimethylsulfide as described in Example 10. The free base was

- 63 -

recrystallised from ether and hexane to give the product as a white crystalline solid. ^1H NMR (250MHz, CDCl_3) δ 1.44-1.64 (2H, m, CH_2), 1.9-2.2 (2H, m, CH_2), 2.24 (1H, d, $J = 7\text{Hz}$, CHN), 3.14 (1H, d, $J = 7\text{Hz}$, CHN), 3.4 (1H, s, CHO), 3.56 (1H, s, NCHPh), 3.6 (1H, s, CH -thiophene), 4.88 (1H, d, $J = 10\text{Hz}$, CH -thiophene), 4.0 (1H, d, $J = 10\text{Hz}$, CHAr), 4.24 (1H, d, $J = 10\text{Hz}$, CHAr), 6.7 (1H, d, $J = 1\text{Hz}$, thiophene-H), 6.9 (H, dd, $J = 2\text{Hz}$, 3Hz , thiophene-H), 7.2 (1H, d, $J = 3\text{Hz}$, thiophene-H), 7.28 (4H, m, Ar-H), 7.5 (3H, m, Ar-H), 7.68 (1H, s, Ar-H). MS m/z 500 (M^+ , 100%).

EXAMPLE 15

5-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinomethyl]-2,3-dihydro-4-methyl-3-thioxo-1,2,4-triazole hydrochloride

A suspension of the compound of Description 7 (0.50g) and methyl isothiocyanate (0.09ml) in 1-butanol (10ml) was heated under reflux for 10 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.1ml) was added and the reaction mixture was heated under reflux for 2.5h. The solvent was removed *in vacuo* and the residue was partitioned between water and ethyl acetate. The organic layer was dried (MgSO_4) and evaporated. The residue was purified on silica using 5% methanol in dichloromethane as eluant to give the title compound. The product (470mg) was characterised as the hydrochloride salt. ^1H NMR (360MHz, $\text{DMSO}-d_6$) δ 1.77-1.93 (2H, m, CH_2), 2.05-2.22 (1H, m, CHH), 2.31 (1H, d, $J = 13.5\text{Hz}$, CHH), 3.42 (3H, s, CH_3), 3.45-3.51 (1H, m, NCHHCH_2), 3.83 (1H, d, $J = 12.0\text{Hz}$, NCHHCH_2), 3.97 (1H, brs, CHO), 4.24 (1H, d, $J = 15.5\text{Hz}$, N-CHH-het), 4.32 (1H, d, $J = 15.5\text{Hz}$,

- 64 -

N-CHH-het), 4.33 (1H, d, J = 12.5Hz, O-CHH), 4.76 (1H, s, NCH), 4.80 (1H, d, J = 12.5Hz, O-CHH), 7.42-7.50 (3H, m, ArH), 7.59 (2H, brs, ArH), 7.85 (2H, s, ArH), 7.89 (1H, s, ArH), 9.15 (1H, brs, NH); MS (FAB) m/z 530 (M+1)⁺, 13%).

5

EXAMPLE 16

3-[(2R*,3R*)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinolmethyl]-1,2,4-triazole

The compound of Description 1 (1.0g), anhydrous
10 potassium carbonate (0.94g) and N-formyl-2-chloroacetamidohydrazone (0.46g), (prepared according to Yanagisawa, I., J. Med. Chem. 1984, 27, 849) were heated to 60°C in anhydrous dimethylformamide for 3h, followed by heating at 130°C for 12h. The reaction mixture was cooled,
15 diluted with ethyl acetate (100ml) and washed with water, (3 x 20ml). The ethyl acetate layer was dried (MgSO₄), filtered and evaporated to give a brown oil. This was purified on silica using ethyl acetate in petrol (70:30) as eluant. This afforded the product as a white solid. ¹H NMR (250MHz, CDCl₃) δ 1.6 (2H, m, CH₂), 1.95-2.24 (2H, m, CH₂), 2.34 (1H, m, NCHH), 3.06 (1H, m, NCHH), 3.44 (1H, d, NCHH-triazole), 3.5 (1H, bs, CHO), 3.6 (1H, bs, NCHPh), 3.8 (1H, d, N-CHH-triazole), 4.04 (1H, d, OCHH-Ar), 4.50 (1H, d, OCHHAr), 7.3 (3H, m, ArH), 7.44 (2H, m, ArH), 7.5 (2H, s, ArH), 7.7 (1H, s, ArH), 7.9 (1H, s, triazole-H). MS (CI⁺) m/z 485 (M⁺+1, 35%).
25

- 65 -

EXAMPLE 17

5-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-2,3-dihydro-(4H)-3-thioxo-1,2,4-triazole

5 The compound of Description 7, potassium thiocyanate (0.45g) and conc. hydrochloric acid (2.3ml) in water (12ml) were heated under reflux for 2h. After cooling, solid sodium hydroxide was added until pH = 8 and the aqueous layer was extracted with ethyl acetate. The organic layer was dried
10 (MgSO₄), filtered and evaporated to give the crude semi-carbazide which was heated at reflux in 2N sodium hydroxide solution (10ml) for 2h. After cooling the solution was acidified to pH 5-6 and the product extracted into ethyl acetate. The organic layer was dried (MgSO₄), filtered and evaporated.
15 The crude triazole was chromatographed on silica eluting with 40% ethyl acetate/60-80 petroleum ether to give the title compound as a white solid. ¹H NMR (250MHz, CDCl₃) δ 1.6 (2H, m, CH₂), 1.9-2.3 (3H, m, CH₂ + NCHH), 2.95 (1H, bd, NCHH), 3.16 (1H, d, N-CHH-Het), 3.20 (1H, bs, CHO), 3.6 (1H, bs, NCHPh), 3.78 (1H, d, N-CHH-Het), 4.1 (1H, d, CHH-Ar), 4.58 (1H, d, CHH-Ar), 7.32 (5H, m, ArH), 7.5 (2H, s, Ar-H), 7.78 (1H, s, ArH). MS (FAB) m/z 517 (M⁺+1, 80%).

EXAMPLE 18

25 5-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-2-methyltetrazole

The compound of Example 7 (500mg) was suspended in water (4ml) and sodium hydroxide (44mg) added. This was

- 66 -

heated to an external temperature of 96°C and dimethyl sulphate (65mg) added. The reaction mixture was allowed to stir under nitrogen at 96°C for 1h after which time stirring was continued for 24h at 5°C. After this time, the product was
5 extracted into dichloromethane and washed with water and brine. The organic layer was dried (MgSO₄) and evaporated. The residue was purified on silica using medium pressure chromatography (Lobar), and eluted with 25% ethyl acetate in petrol. The first compound to be eluted was isolated, and this
10 afforded the product (50mg) as a crystalline solid, which was recrystallised from ether/hexane to afford white crystals: mp 139-141°C. ¹H NMR (360MHz, DMSO) δ 1.44-1.51 (2H, m, CH₂), 1.79-1.82 (1H, m, CHH), 2.12-2.15 (1H, m, CHH), 2.19-2.25 (1H, m, CHHN), 2.97-3.00 (1H, m, CHHN), 3.37 (1H, d, J = 14Hz, N-CHH-tetrazole), 3.52 (1H, s, NCHCHO), 3.58 (1H, s, NCHCHO), 3.81 (1H, d, J = 14Hz, N-CHH-tetrazole), 4.03 (1H, d, J = 13Hz, OCHH), 4.31 (3H, s, CH₃), 4.60 (1H, d, J = 13Hz, OCHH), 7.23-7.33 (3H, m, ArH), 7.49-7.51 (2H, m, ArH), 7.68 (2H, s, ArH), 7.93 (1H, s, ArH); MS (CI⁺) m/z 500 (M+1)⁺, 100%. Found: C, 55.56; H, 4.76; N, 14.20. Calculated for C₂₃H₂₃N₅O₆: C, 55.31; H, 4.64; N, 14.02%.

EXAMPLE 19

25 5-[(2R*,3R*)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinolmethyl]-1-methyltetrazole

The title compound was prepared as described in Example 18. During purification, the second compound to be eluted was isolated, and this afforded the product (120mg) as a crystalline solid, which was recrystallised from ether/hexane to

- 67 -

afford yellow crystals: mp 75-77°C. ¹H NMR (360MHz, DMSO) d 1.51-1.55 (2H, m, CH₂), 1.84-1.87 (1H, m, CHH), 2.12-2.16 (1H, m, CHH), 2.31-2.37 (1H, m, CHHN), 2.81-2.84 (1H, m, CHHN), 3.52 (1H, d, J = 15Hz, NCHH-tet), 3.54 (1H, s, NCHCHO), 3.60 (1H, s, NCHCHO), 3.82 (1H, d, J = 14Hz, NCHH-tet), 3.84 (3H, s, CH₃), 4.14 (1H, d, J = 13Hz, OCHH), 4.85 (1H, d, J = 13Hz, OCHH), 7.26-7.32 (3H, m, ArH), 7.45-7.48 (2H, m, ArH), 7.74 (2H, s, ArH), 7.94 (1H, s, ArH); MS (CI⁺) m/z 500 ((M+1)⁺, 20%).

10

EXAMPLE 20

3-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-5-dimethylamino-1,2,4-thiadiazole

15

a) 5-Dimethylamino-3-(chloromethyl)-1,2,4-thiadiazole

A solution of dimethylamine in ethanol (0.5ml x 33%) was added to a stirred suspension of 5-chloro-3-(chloromethyl)-1,2,4-thiadiazole (540mg) (J. Goerdeler, Chem. Ber. 1957, 90, p 182 or ICI EP 0006679) and potassium carbonate (1.0g) in methanol. The solution was stirred at room temperature for three hours, and then the solvent removed under reduced pressure. The residue was taken up in ethyl acetate (40ml), washed with water (20ml) and brine (20ml). The organic layers were dried (MgSO₄), filtered and the solvent removed to afford a yellow gum. Flash chromatography using 10% ethyl acetate in hexane as eluent, afforded the product as a yellow oil (330mg). ¹H NMR (360MHz, CDCl₃) d 3.15 (6H, s, N(CH₃)₂), 4.51 (2H, s, Cl-CH₂); MS (CI⁺) m/z 178 ((M+1)⁺, 95%).

25

b) A solution of the compound of Description 1 (223mg), 5-dimethylamino-3-(chloromethyl)-1,2,4-thiadiazole (100mg)

30

- 68 -

and diisopropylethylamine (0.2ml) were heated at reflux in dry acetonitrile for three hours. The reaction was then allowed to cool to room temperature and the solvent removed under reduced pressure. Purification of the residue by flash chromatography (40% EtOAc/nHex) gave a yellow gum. Recrystallisation from n-hexane afforded the product as yellow plates: mp 144-145°C. ¹H NMR (360MHz, CDCl₃) δ 1.57 (2H, m, CH₂), 2.11 (3H, m, CH₂+CHH), 2.42 (1H, m, CHH), 3.11 (6H, s, N(CH₃)₂), 3.20 (1H, m, CH-OCH₂), 3.47 (1H, d, J = 14.5Hz, CHH-thiadiazole), 3.56 (1H, m, CHPh), 3.75 (1H, d, J = 14.5Hz, CHH-thiadiazole), 4.03 (1H, d, J = 10.5Hz, OCHH-Ar), 4.45 (1H, d, J = 10.5Hz, OCHH-Ar), 7.30 (3H, m, ArH), 7.51 (2H, s, ArH), 7.53 (2H, m, ArH), 7.69 (1H, s, ArH); MS (CI⁺) m/z 545 ((M+1)⁺, 60%). Found: C, 55.12; H, 4.75; N, 10.38. Calcd. for C₂₅H₂₀F₆N₄SO: C, 55.14; H, 4.81; N, 10.30%.

EXAMPLE 21

2-[(2R*,3R*)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinolmethyl]-4,7-dimethylbenzoxazole

A solution of 2-(chloromethyl)-4,7-dimethylbenzoxazole (285mg) in dry acetonitrile (10ml) was added to a solution of the compound of Description 1 in dry acetonitrile (10ml) containing diisopropylethylamine (0.4ml). The resulting mixture was heated at reflux for three hours, cooled to room temperature and the residue purified by flash chromatography on silica gel using 20% ethyl acetate/n-hexane as eluant. Recrystallisation of the isolated material from n-hexane afforded the product as white needles: mp 109-110°C. ¹H NMR (CDCl₃) 1.49-1.53 (2H, m, CH₂), 1.56-1.60 (1H, m, CHH), 2.03-2.09 (1H, m, CHH), 2.10-2.16 (1H, m, CHHN), 2.36-2.40 (1H, m, CHHN), 2.47 (3H,

- 69 -

s, Ar-CH₃), 2.54 (3H, s, ArCH₃), 3.24 (1H, m, CHN), 3.59 (1H, m, CHOCH₂), 3.67 (1H, d, J = 12.0Hz, N-CHH-benzoxazole), 3.79 (1H, d, J = 12.0Hz, N-CHH-benzoxazole), 3.96 (1H, d, J = 10.0Hz, OCHH), 4.47 (1H, d, J = 10.0Hz, OCHH), 6.99 (2H, s, ArH), 7.32 (3H, m, ArH), 7.54 (2H, s, ArH), 7.57 (2H, m, ArH), 7.71 (1H, s, ArH); MS (CI⁺) m/z 563 ((M+1)⁺, 70%). Found: C, 64.09; H, 5.04; N, 5.12. Calcd for C₃₀H₂₈N₂O₂F₆: C, 64.05; H, 5.01; N, 5.00%.

10

EXAMPLE 22

2-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidinolmethyl]benzoxazole

This compound was prepared following the procedure described in Example 21, using 2-(chloromethyl)benzoxazole as the alkylating agent: mp 95-97°C. ¹H NMR (CDCl₃) δ 1.47-1.60 (2H, m, CH₂), 2.06-2.19 (2H, m, CH₂), 2.42-2.56 (1H, dd, 1H, J = 6.0, 4.0Hz, NCHH), 3.26 (1H, dd, J = 4.0, 2.0Hz, NCHH), 3.61 (1H, s, CHO), 3.66 (1H, d, J = 15.0Hz, NCHH-benzoxazole), 3.66 (1H, d, J = 2.0Hz, CHPh), 4.02 (1H, d, J = 15.0Hz, CHH-benzoxazole), 4.04 (1H, d, J = 12.0Hz, OCHH), 4.48 (1H, d, J = 12.0Hz, OCHH), 7.26-7.67 (12H, m, ArH); MS (CI⁺) m/z 535 ((M+1)⁺ 65%). Found: C, 62.36; H, 4.67; N, 5.27. Calc for C₂₈H₂₄F₆N₂O₂ · 1/4 H₂O: C, 62.39; H, 4.58; N, 5.20%.

25

EXAMPLE 23

4-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidinolmethyl]oxazole

- 70 -

1,3-oxazole-4-carboxaldehyde was prepared following the procedure described by J. Hodges, W. Patt and C. Connolly, J. Org. Chem. 1991, 56, 449-452.

5 a) 4-(Hydroxymethyl)-1,3-oxazole

1,3-Oxazole-4-carboxaldehyde (0.38g) was dissolved in anhydrous methanol and stirred under nitrogen; sodium borohydride (0.074g) was added carefully. After 1 hour no starting material was present by TLC using 50% ethyl acetate
10 in hexane as eluent. The methanol was removed by rotary evaporator (water bath temp 40°C). The residue was purified by chromatography on silica eluting with 100% diethyl ether. This afforded the alcohol (0.27g) as a white solid. ¹H NMR d (360 MHz, CDCl₃) 2.93 (OH), 4.63 (2H, s, CH₂OH), 7.64 (1H, s, oxazole-H), 7.90 (1H, s, oxazole-H).

15 b) 4-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol]methylloxazole

4-(Hydroxymethyl)-1,3-oxazole (0.13g) was dissolved in anhydrous dichloromethane (4ml) under an atmosphere of
20 nitrogen. Triethylamine (0.19ml) and *p*-toluenesulfonyl chloride (0.13g) were added to the reaction mixture which was stirred for 1 hour at room temperature. A further portion of *p*-toluenesulfonyl chloride (0.13g) and a catalytic amount of dimethylaminopyridine were added to the reaction mixture.
25 The compound of Description 3 (1.2g, free base) was dissolved in dimethylformamide (5ml) and was added to the reaction mixture followed by triethylamine (0.19ml). The mixture was heated at 60°C for 2h and the resulting mixture was diluted with water (50ml) and extracted with dichloromethane (3 x 20ml). The
30 combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to afford a yellow oil. This was purified by

- 71 -

chromatography on silica gel using a gradient elution of 30-60% ether in hexane to afford the title compound as a white solid. This was recrystallised from ether/hexane: mp 102-104°C. ¹H NMR (360MHz, CDCl₃) δ 1.46-1.64 (1H, m, NCH₂CH₂CHH), 1.7-1.87 (1H, m, NCH₂CH₂CHH), 1.96-2.20 (2H, m, NCH₂CH₂), 2.32-2.48 (1H, m, NCHH), 3.20-3.46 (3H, m, NCHH + NCHH-oxazole + CHOCH₂Ar), 3.55 (1H, brs, CHPh), 3.68 (1H, d, J = 14.5Hz, NCHH-oxazole), 4.01 (1H, d, J = 11.5Hz, OCHHAr), 4.46 (1H, d, J = 11.5Hz, OCHHAr), 7.24-7.58 (8H, m, ArH), 7.70 (1H, s, ArH), 7.80 (1H, s, ArH); MS (CI⁺) 485 (M⁺ + 1, 100%)

EXAMPLE 24

2-[1(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl]pyrazine

a) 2-(Chloromethyl)pyrazine

2-Methylpyrazine (1g) was dissolved in carbon tetrachloride (50ml) under nitrogen. N-Chlorosuccinimide (1.42g) and benzoyl peroxide (50mg) were added and the mixture was heated at reflux for 24h. The reaction mixture was cooled and filtered through celite and the filtrate was concentrated *in vacuo*. The resulting oil was purified on silica using 30% ethyl acetate in petrol. ¹H NMR (360MHz, CDCl₃) δ 4.72 (2H, s, CH₂Cl), 8.56 (2H, s, ArH), 8.76 (1H, s, ArH).

b) 2-[1(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl]pyrazine

2-(Chloromethyl)pyrazine (0.17g), potassium carbonate (0.6g) and the compound of Description 3 (0.35g) were suspended in dimethylformamide (3ml); the reaction mixture was heated at 60°C for 12h. The mixture was cooled, diluted

- 72 -

with water (30ml) and extracted with ethyl acetate (2 x 20ml). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil. The product was purified by column chromatography on silica gel using a gradient elution of 15-35% ethyl acetate in hexane. This afforded the product as a white solid, which was recrystallised from pentane to give colourless crystals: mp 108-110°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.42-1.60 (2H, m, NCH₂CH₂CH₂), 1.77-1.92 (1H, m, NCH₂CHH), 2.13-2.25 (2H, m, NCHH + NCH₂CHH), 2.84-2.92 (1H, m, NCHH), 3.12 (1H, d, J = 14.0Hz, NCHH-pyrazine), 3.55 (1H, m, CHO), 3.63 (1H, m, CHPh), 3.78 (1H, d, 14.0Hz, NCHH-pyrazine), 4.11 (1H, d, J = 13.0Hz, OCHHAr), 4.64 (1H, d, J = 13.0Hz, OCHHAr), 7.20-7.33 (3H, m, ArH), 7.49-7.56 (2H, m, ArH), 7.71 (2H, s, ArH), 7.93 (1H, s, ArH), 8.48-8.63 (3H, m, ArH); MS (CI⁺) 496 (M⁺+1, 60%). Found: C, 60.90; H, 4.86; N, 8.48. Calcd. for C₂₅H₂₃F₆N₃O: C, 60.60; H, 4.68; N, 8.48%.

EXAMPLE 25

4-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino]methyl-2-methyl-1,3-thiazolium dihydrochloride

4-(Chloromethyl)-2-methylthiazole hydrochloride (83mg) was added to a suspension of the compound of Description 3 and potassium carbonate in dimethylformamide (5ml). The resulting mixture was heated at 60°C for 18h, cooled to room temperature and diluted with water (50ml). This solution was extracted with ethyl acetate (2 x 25ml) and the combined organic extracts were washed with water (2 x 20ml), brine (20ml), dried (MgSO₄) and filtered. The resulting solution was

- 73 -

evaporated under reduced pressure to afford a yellow oil. This was purified by medium pressure liquid chromatography using 50% ethyl acetate in hexane to afford the product as a white solid. This was treated with ethereal hydrogen chloride and recrystallised from methyl-*t*-butyl ether to afford the title compound: mp 58-60°C. ¹H NMR (360MHz, DMSO-*d*₆) δ 1.71 (2H, m, CH₂), 2.11 (2H, mc, CH₂), 2.49 (1H, m, CHHN), 2.69 (3H, s, Ar-CH₃), 3.15 (1H, m, CHHN), 3.54 (1H, m, CHO), 4.12 (2H, m, CH₂-thiazole), 4.16 (1H, d, J = 10.0Hz, OCHHAr), 4.58 (1H, brs, CHPh), 4.76 (1H, d, J = 10.0Hz, OCHHAr), 7.40-7.43 (5H, m, ArH), 7.64 (1H, brs, ArH), 7.92 (2H, s, ArH), 7.97 (1H, s, ArH); MS (CI⁺) m/z 515 (M⁺ + 1). Found: C, 48.17; H, 4.76; N, 4.52. Calcd. for C₂₅H₂₄F₆N₂OS.2HCl.2H₂O: C, 48.16; H, 4.85; N, 4.49%.

EXAMPLE 26

3-[[[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl]-1,2,4-oxadiazole hydrochloride

3-(Chloromethyl)-1,2,4-oxadiazole (270mg) was added to a rapidly stirred suspension of the compound of Description 3 and potassium carbonate in dimethylformamide (10ml). The reaction mixture heated at 60°C for 4h, cooled to room temperature and diluted with water (50ml). The aqueous solution was extracted with ethyl acetate (3 x 50ml) and the organic extracts were combined, washed with water (3 x 50ml), brine (50ml), dried (MgSO₄) and filtered. The resulting solution was concentrated under reduced pressure and purified by column chromatography on silica gel using 20% ethyl acetate in hexane as eluent. The resulting oil was treated with ethereal hydrogen chloride to afford the title compound as a white

- 74 -

powder: mp 74-75°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.62 (2H, m, CH₂), 1.97-2.1 (2H, m, CH₂), 2.50 (1H, m, CHHN), 3.16 (1H, m, CHHN), 3.51 (1H, m, CHQ), 3.69-3.72 (3H, m, CH₂-oxadiazole + CHPh), 4.14 (1H, d, J = 10.0Hz, OCHHAr), 4.70 (1H, d, J = 10.0Hz, OCHHAr), 7.32 (3H, m, ArH), 7.45 (2H, m, ArH), 7.78 (3H, m, ArH), 7.94 (1H, s, ArH).

EXAMPLE 27

10 3-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-5-iodo-1,2,4-thiadiazole

a) 5-Iodo-3-(iodomethyl)-1,2,4-thiadiazole

15 Sodium iodide (excess) was added to a stirred solution of 5-chloro-3-(chloromethyl)-1,2,4-thiadiazole (3.0g) (J. Goerdeler, Chem. Ber. 1957, 90, 182) in dry butanone (15ml). The resulting solution was heated at reflux for four hours, cooled to room temperature and filtered. The filtrate was diluted with water (20ml) and extracted with ethyl acetate (50ml). The ethyl acetate layer was dried (MgSO₄), filtered and concentrated *in vacuo* to afford a red oil, which was used in the following reaction without further purification.

20 b) 3-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-5-iodo-1,2,4-thiadiazole

25 Diisopropylethylamine (116mg) was added to a stirred solution of 5-iodo-3-(iodomethyl)-1,2,4-thiadiazole (160mg) and the compound of Description 3 (200mg) in dry acetonitrile (10ml). The resulting solution was stirred at room temperature for 18h. The reaction mixture was filtered and the solvent was removed *in vacuo* to afford a red oil. This was purified using column chromatography on silica gel using 20% ethyl acetate in hexane as eluent. This afforded the product as a powder: mp

30

- 75 -

98-101°C. ¹H NMR (360MHz, CDCl₃) δ 1.55 (3H, m, NCH₂CH₂CH₂ + NCH₂CHH), 2.13 (2H, m, NCH₂CHH + NCHH), 2.42 (1H, m, CHHN), 3.21 (1H, m, CHO), 3.69 (2H, m, CHPh + CHH-thiadiazole), 4.02 (2H, m, CHH-thiadiazole + OCHH), 4.48 (1H, d, J = 8.0Hz, OCHH), 7.32 (5H, m ArH), 7.51 (2H, s ArH), 7.70 (1H, s, ArH).

EXAMPLE 28

10 3-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinylmethyl]-1,2,4-thiadiazole hydrochloride

Sodium borohydride (280mg) was added to a stirred solution of the compound of Example 27 (500mg) and palladium (II) chloride (280mg) in dry methanol (25ml). The resulting mixture was stirred for 30 min and then filtered through celite; the filtrate was concentrated *in vacuo*. The solid residue thus obtained was dissolved in ethyl acetate and the solution was washed with water (10ml), the organic extract was dried (MgSO₄), filtered and concentrated *in vacuo* to afford a yellow oil. Treatment of this oil with ethereal hydrogen chloride afforded the title compound as a white powder: mp 89-90°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.79 (2H, m, CH₂), 1.9-2.20 (3H, m, CHHN + NCH₂CH₂), 2.6 (1H, m, CHHN), 3.8 (1H, bm, CHO), 3.89 (1H, brs, CHPh), 4.2-4.3 (3H, m, CH₂-thiadiazole + OCHH), 4.76 (1H, d, J = 9.0Hz, OCHH), 7.39 (3H, m, ArH), 7.55 (2H, m, ArH), 7.89 (2H, s, ArH), 8.32 (1H, s, ArH), 10.32 (1H, s, N-CH-S); MS (CI⁺) m/z 502 (M⁺ + 1). Found: C, 49.31; H, 4.09; N, 7.18%. Calcd. for C₂₃H₂₁F₆N₃OS.HCl.1.25H₂O : C, 49.48; H, 4.37; N, 7.52%.

- 76 -

EXAMPLE 293-[[[(2S,3S)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinolmethyl]-5-methoxy-1,2,4-thiadiazole hydrochloride

5 Sodium methoxide (34mg) was added to a stirred solution of the compound of Example 27 (200mg) in methanol (5ml). The solution was heated at reflux for 2h, cooled to room temperature and the solvent removed under reduced pressure affording a solid residue. The solid was dissolved in ethyl acetate (15ml),
10 and the organic phase was washed with water (20ml), separated, dried (MgSO₄) and the solvent was removed under reduced pressure. The residual solid was treated with ethereal hydrogen chloride and the resulting solid was recrystallised from ethyl acetate to afford the product as white needles: mp
15 74-75°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.55 (2H, m, CH₂), 1.73 (1H, m, CHH), 2.09 (2H, m, CH₂), 2.43 (1H, m, CHH), 3.20 (1H, m, CHO), 3.49 (2H, m, CHPh + CHH-thiadiazole), 3.75 (1H, m, CHH-thiadiazole), 4.02 (1H, d, J = 10.0Hz, OCHH), 4.14 (3H, s, OCH₃), 4.45 (1H, d, J = 10.0Hz, OCHH), 7.30 (3H, m, ArH),
20 7.51 (4H, brs, ArH), 7.54 (1H, s, ArH); MS (CI⁺) m/z 532 (M⁺ + 1). Found: C, 49.89; H, 4.10; N, 7.41. Calcd. for C₂₄H₂₃F₆N₃O₂S.HCl.0.5H₂O: C, 49.96; H, 4.37; N, 7.28%.

EXAMPLE 30

25 3-[[[(2S,3S)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinolmethyl]-1,2,4-triazole dihydrochloride

The title compound was prepared according to the procedure described in Example 16, using the compound of

- 77 -

Description 3 as starting material. The free base was treated with ethereal hydrogen chloride to afford the product as a white crystalline solid: mp (free base) 209-210°C. Found: C, 49.36; H, 4.57; N, 10.05. Calcd. for $C_{23}H_{22}F_6N_4O \cdot 2HCl$: C, 49.56; H, 4.34; N, 10.05%.

EXAMPLE 31

5-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-2,3-dihydro-(4H)-3-thioxo-1,2,4-triazole hydrochloride

The title compound was prepared according to the procedure described in Example 17, using the compound of Description 8 as a starting material. This afforded the product as a white solid which was treated with ethereal hydrogen chloride to yield the crystalline hydrochloride: mp 154-157°C. Found: C, 46.59; H, 4.52, N, 9.26; Cl, 5.84. Calcd. for $C_{23}H_{22}F_6N_4O \cdot HCl \cdot 2H_2O$: C, 46.90; H, 4.62; N, 9.51; Cl, 6.02%.

EXAMPLE 32

2-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-1-(p-toluenesulfonyl)imidazole dihydrochloride

(a) N-(p-Toluenesulfonyl)imidazole-2-carboxaldehyde.

Imidazole-2-carboxaldehyde (1.92g) was suspended in dichloromethane (20ml). p-Toluenesulfonyl chloride (3.8g) and triethylamine (2.8ml) were added to the mixture which was stirred at room temperature for 12 hours. The resulting slurry was diluted with water and the organic layer was washed with

- 78 -

brine, dried (MgSO_4) and filtered. The dichloromethane layer was concentrated *in vacuo* and the residue was purified by column chromatography on silica using 50% ethyl acetate in hexane as eluent. This afforded the product as a yellow oil which crystallised on standing. ^1H NMR (360MHz, CDCl_3) δ 2.44 (3H, s, ArCH_3), 7.31 (1H, d, $J=1.5\text{Hz}$, imidazole-H), 7.37 (2H, d, $J=8.0\text{Hz}$, ArH), 7.83 (1H, d, $J=1.5\text{Hz}$, imidazole-H), 8.00 (2H, d, $J=8.0\text{Hz}$, ArH), 9.78 (1H, s, CHO). MS (Cl^+) m/z 251 (M^++1).

10 (b) 2-(Hydroxymethyl)-1-(p-toluenesulfonyl)imidazole

The aldehyde of (a) above (3g) was dissolved in methanol (15ml) and sodium borohydride (114mg) was added portionwise. This solution was stirred for 10 min. Methanol was removed *in vacuo* and the residue was dispersed between ethyl acetate and water. The organic layer was separated, dried (MgSO_4) and filtered and the solvent was removed *in vacuo* to afford a crystalline solid. ^1H NMR (250MHz, CDCl_3) δ 2.42 (3H, s, ArCH_3), 4.84 (2H, s, CH_2O), 7.00 (1H, d, $J=1.5\text{Hz}$, imidazole-H), 7.36 (2H, d, $J=8.0\text{Hz}$, ArH), 7.40 (1H, d, $J=1.5\text{Hz}$, imidazole-H), 7.84 (2H, d, $J=8.0\text{Hz}$, ArH).

20 (c) ((N-p-Toluenesulfonyl)imidazol-2-yl)methyl methanesulfonate

The alcohol described in (b) above (12.6mg) was dissolved in dichloromethane (2.5ml) and triethylamine (.07ml). This solution was cooled to 0°C . Methanesulfonyl chloride (.04ml) was added to the solution dropwise. After stirring for 10 mins the solution was diluted with water and the organic layer was separated, dried (MgSO_4), filtered and the solvent removed *in vacuo* to yield a white solid which was used in the following reaction without further purification. ^1H NMR (250MHz, CDCl_3) δ 2.44 (3H, s, ArH), 2.94 (3H, s, SO_2CH_3), 5.51 (2H, s,

- 79 -

CH_2SO_2), 7.08 (1H, d, $J=1.5\text{Hz}$, imidazole-H), 7.40 (2H, d, $J=8.0\text{Hz}$, ArH), 7.49 (1H, d, $J=1.5\text{Hz}$, imidazole-H), 7.92 (2H, d, $J=8.0\text{Hz}$, ArH).

(d) ((N-*p*-Toluenesulfonyl)imidazol-2-yl)methylmethane-sulfonate (1.6g) was added to a suspension of the compound of Description 3 (2.47g) and potassium carbonate (800mg) in dimethylformamide (10ml) and the resulting mixture was heated at 100°C for 2h. The mixture was cooled, diluted with water (100ml) and extracted with ethyl acetate (3 x 20ml). The organic extracts were combined, washed with brine, dried (MgSO_4) and concentrated *in vacuo*. This afforded a colourless oil which was purified by column chromatography on silica using 25-30% ethyl acetate in hexane. This afforded the product as a white crystalline solid which was recrystallised from dichloromethane/petrol: mp $125-126^\circ\text{C}$. ^1H NMR (360MHz, $\text{DMSO}-d_6$) δ 1.4-1.5 (1H, m, $\text{NCH}_2\text{CH}_2\text{CHH}$), 1.5-1.67 (1H, m, $\text{NCH}_2\text{CH}_2\text{CHH}$), 1.8-2.0 (1H, m, NCH_2CHH), 2.06-2.1 (1H, m, NCH_2CHH), 2.35 (3H, s, CH_3), 2.4 (1H, mc, NCHH), 2.7-2.86 (1H, m, NCHH), 3.50 (1H, d, $J = 14.0\text{Hz}$, CHH-imidazole), 3.56 (1H, brs, CHO), 3.76 (1H, d, $J = 1.5\text{Hz}$, CHPh), 4.08 (1H, d, $J = 14.0\text{Hz}$, CHH-imidazole), 4.09 (1H, d, $J = 12.0\text{Hz}$, OCHH), 4.48 (1H, d, $J = 12.0\text{Hz}$, OCHH), 6.96 (1H, d, $J = 1.0\text{Hz}$, imidazole-H), 7.12 (2H, d, $J = 8.5\text{Hz}$, ArH), 7.2-7.3 (3H, m, ArH), 7.34 (1H, d, $J = 1.0\text{Hz}$, imidazole-H), 7.46-7.58 (2H, m, ArH), 7.60 (2H, s, ArH), 7.71 (1H, ArH), 7.79 (2H, d, $J = 8.5\text{Hz}$, ArH); MS (CI^+) m/z 638 ($\text{M}^+ + 1$). Found: C, 58.48; H, 4.78; N, 6.72; S, 4.81. Calcd. for $\text{C}_{31}\text{H}_{29}\text{F}_6\text{N}_3\text{O}_3\text{S}$: C, 58.39; H, 4.58; N, 6.59; S, 5.03%.

30

- 80 -

EXAMPLE 332-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methylimidazole dihydrochloride

The compound of Example 32 was dissolved in dichloromethane and ethereal hydrogen chloride was added. The resulting solution was stirred for 30 minutes whereupon the title compound crystallised from solution. This was removed by filtration and recrystallised from ethyl acetate/methanol to afford the title compound as a white crystalline compound. ¹H NMR (360MHz, D₂O) δ 1.61-1.74 (1H, m, CHH), 1.76-1.88 (1H, m, CHH), 2.04-2.21 (2H, m, CH₂), 3.07-3.23 (1H, m, NCHH), 3.41-3.51 (1H, m, NCHH), 3.66 (1H, s, CHO), 4.09 (1H, d, J=13.0Hz, OCHH), 4.25 (1H, d, J=15.5Hz, CHH-imidazole), 4.30 (1H, s, CHPh), 4.39 (1H, d, J=15.5Hz, CHH-imidazole), 4.55 (1H, d, J=13.0Hz, OCHH), 7.1-7.2 (3H, m, ArH), 7.2-7.3 (2H, m, ArH), 7.38 (2H, s, imidazole-H), 7.48 (2H, s, ArH), 7.51 (1H, s, ArH); MS (Cl⁺) m/z 484 (M⁺+1, 25%). Found: C, 50.32; H, 4.92; N, 7.23; Cl, 12.58. Calcd. for C₂₄H₂₃F₆N₃O.2HCl.H₂O: C, 50.18; H, 4.74; N, 7.32; Cl, 12.34%.

EXAMPLE 344-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methylimidazole dihydrochloride

This was prepared following the procedure described for Example 33 using the compound of Description 3 and 4-(hydroxymethyl)imidazole as starting materials. This afforded the title compound as a white crystalline compound: mp 206-210°C. ¹H NMR (360MHz, D₂O) δ 1.73 (1H, m,

- 81 -

NCH₂CH₂CHH), 1.94-2.06 (1H, m, NCH₂CH₂CHH), 2.22-2.40 (2H, m, NCH₂CH₂), 3.33 (1H, mc, NCHH), 3.70-3.81 (1H, m, NCHH), 3.97 (1H, brs, CHO), 4.30 (1H, d, J=12.5Hz, OCHH), 4.42(2H, s, NCH₂-imidazole), 4.50 (1H, s, NCHPh), 4.75 (1H, d, J=12.5Hz, OCHH), 7.48 (6H, brs, ArH+imidazole-H), 7.74 (2H, s, ArH), 7.95 (1H, s, ArH), 8.80 (1H, s, imidazole-H); MS (CI⁺) m/z 484 (M⁺+1 Found: C, 50.22; H, 4.82; N, 7.18; Cl, 12.49. Calcd. for C₂₄H₂₃F₆N₃O.2HCl.H₂O: C, 50.18; H, 4.74; N, 7.32; Cl, 12.34%

10

EXAMPLE 35

5-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole hydrochloride

15

(a) N-Carbomethoxy-2-chloroacetamidrazone

Sodium methoxide (0.032g) was added to a solution of chloroacetonitrile (1.26ml) in anhydrous methanol (15ml) at 0°C. The reaction mixture was stirred at room temperature for 0.5 hour and then neutralised with acetic acid (0.034ml). Methyl hydrazinocarboxylate (1.79g) was added and the reaction mixture stirred at room temperature for 0.5 hour. The solution was concentrated *in vacuo* to give the title compound as an orange solid. MS (CI)⁺ m/z 166.

20

(b) The compound of Description 1 (0.50g) was stirred with N-carbomethoxy-2-chloroacetamidrazone (0.19g) and potassium carbonate (0.47g) in dimethylformamide (10ml) at 70°C for 18 hours. The reaction mixture was then stirred at 140°C for 1 hour. After cooling, the material was partitioned between ethyl acetate and water. The organic layer was washed

25
30

- 82 -

with water, dried (MgSO_4), filtered and concentrated. The residue was purified by chromatography on silica using 5% methanol in ethyl acetate as eluent. The product was recrystallised from ethyl acetate/petrol to give the title compound as a white crystalline solid. This was characterised as its hydrochloride salt: mp 168-172°C. MS (CI^+) m/z 500 ($(\text{M}+1)^+$, 18%). Found: C, 50.65; H, 4.43; N, 10.22; Cl, 6.71. Calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_{2.5}\text{F}_6\text{Cl}$: C, 50.60; H, 4.43; N, 10.26; Cl, 6.49%.

EXAMPLE 36

5-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidin-1-yl]-3-(N,N-dimethylamino)-1,2,4-thiadiazole]

(a) 5-(N,N-Dimethylamino)-1,3,4-oxathiazolin-2-one

A solution of chlorocarbonylsulphenyl chloride (11.5g) in acetonitrile was added to a suspension of N,N-dimethylurea (25.0g) in acetonitrile (200ml), over a period of 20 minutes. The reaction mixture was stirred for 1 hour at 23°C, then filtered. Methanol (20ml) was added to the filtrate to decompose excess chlorocarbonylsulphenyl chloride. The solvents were removed *in vacuo*. The residue was purified by chromatography on silica using dichloromethane in hexane (3:1) to afford the product as a yellow oil. ^1H NMR (250MHz, CDCl_3) δ 3.04 (6H, s, $(\text{CH}_3)_2$); MS (CI^+) m/z 164 ($\text{M}^+ + \text{NH}_4^+$)

(b) 5-(Chloromethyl)-3-(N,N-dimethylamino)thiadiazole

Chloroacetonitrile (1.3ml) in dimethylformamide (1ml) was heated to 150-155°C and 5-(N,N-dimethylamino)-1,3,4-oxathiazolin-2-one (1.0g) was added in portions. After 5 minutes the reaction mixture was cooled and concentrated *in*

- 83 -

vacuo. The residue was purified by chromatography on silica using hexane/ethyl acetate (9:1) as eluent. This afforded the product as a white crystalline solid. ¹H NMR (250MHz, CDCl₃) δ 3.19 (6H, s, (CH₃)₂), 4.82 (2H, s, CH₂); MS (CI⁺) m/z 178

5 (c) 5-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-3-(N,N-dimethylamino)-1,2,4-thiadiazole hydrochloride

10 The compound of Description 1 was reacted with 5-(chloromethyl)-3-(N,N-dimethylamino)thiadiazole according to the procedure described in Example 4. This afforded the title compound as a white solid: mp 160-161°C; ¹H NMR (360MHz, DMSO-d₆ + TFA) δ 1.69-1.87 (2H, m, CH₂), 2.01-2.26 (2H, m, CH₂), 3.10 (6H, s, (CH₃)₂), 3.22-3.34 (1H, m, CHH), 3.64-3.72 (1H, m, CHH), 3.90 (1H, s, CHO), 4.26-4.34 (2H, m, CH₂), 4.61 (1H, d, J=20.0Hz, OCHH), 4.76-4.82 (2H, m, OCHH + CHPh), 7.36-7.62 (5H, m, ArH), 7.87 (2H, s, ArH), 7.99 (1H, s, ArH).

EXAMPLE 37

20 5-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]tetrazole

25 This compound was prepared according to the procedure described in Example 7, using the compound of Description 9 as a starting material: mp 179-181°C. MS (CI⁺) m/z 486 (MH⁺, 35%). Found: C, 54.61; H, 4.53; N, 14.37. Calcd. for C₂₂H₂₁F₆N₅O: C, 54.43; H, 4.36; N, 14.43%.

- 84 -

EXAMPLE 38**5-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-2-methyltetrazole**

This compound was prepared according to the procedure described in Example 18 using the compound of Example 37 as a starting material. This afforded the title compound as a white crystalline material: mp 158-159°C. MS (CI^+) m/z 500 (MH^+ , 70%). Found: C, 55.84; H, 4.66, N, 14.13. Calcd. for $\text{C}_{23}\text{H}_{23}\text{F}_6\text{N}_5\text{O}$: C, 55.31; H, 4.64; N, 14.02%.

EXAMPLE 39**5-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-1-methyltetrazole**

This compound was prepared according to the procedure described in Example 19 using the compound of Example 37 as a starting material. This afforded the title compound as a clear oil. MS (CI^+) 500 (MH^+ , 40%). Found: C, 55.27; H 4.69; N, 13.67. Calcd. for $\text{C}_{23}\text{H}_{23}\text{F}_6\text{N}_5\text{O}$: C, 55.31; H, 4.64; N, 14.02%.

EXAMPLE 40**3-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]pyridazine****(a) 3-(Hydroxymethyl)-1,2-pyridazine**

1,2-pyridazine-3-carboxaldehyde (0.89g) (G. Heinisch, E. Luszczak and M. Pailer, Mh. Chem 104, 1372 (1973)) was dissolved in water and sodium borohydride (0.081g) was added carefully. After 1 hour no starting material was present by TLC

- 85 -

using 10% methanol in dichloromethane as eluent. The water was removed *in vacuo* to afford a gum. The gum was extracted with dichloromethane, the combined organics were dried (MgSO₄) and concentrated *in vacuo* to afford the alcohol as a solid, which was used in the following experiment without further purification. ¹H NMR (360MHz, CDCl₃) δ 5.04 (2H, s, CH₂OH), 7.54 (1H, dd, pyridazine-H), 7.65 (1H, dd, pyridazine-H), 9.17 (1H, dd, pyridazine-H).

(b) 3-((2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methylpyridazine

3-(Hydroxymethyl)-1,2-pyridazine was dissolved in anhydrous dichloromethane under an atmosphere of nitrogen and cooled in an ice/water bath. Triethylamine (0.68ml) and methanesulfonyl chloride (0.378ml) were added and the reaction stirred for 1 hour. No starting material was present by TLC using 5% methanol in dichloromethane as eluent. The solvent was removed *in vacuo* to afford a solid. The compound of Description 3 (0.48g of free base) was dissolved in dimethylformamide (5ml) and added to the solid followed by potassium carbonate (0.85g). The mixture was heated at 60°C for 12 hours then poured into water (75ml), extracted with ethyl acetate (3x40ml), dried (MgSO₄) and concentrated to afford a brown oil. This was purified by chromatography on silica gel using a gradient elution of 10-30% ethyl acetate in petrol. Further purification was carried out by medium pressure chromatography; elution with 50/50 ethyl acetate/petrol afforded the title compound as a white solid: mp 111-113°C. ¹H NMR δ (360MHz, DMSO-d₆) 1.43-1.66 (2H, m, NCH₂CH₂CH₂), 1.77-1.91 (1H, m, NCH₂CHH), 2.13-2.24 (2H, m, NCHHCHH), 2.75-2.87 (1H, NCHH), 3.27-3.35 (1H, d, NCHH-pyridazine), 3.57-3.70 (2H, NCHPh + CHO), 3.83-3.93 (1H, d,

- 86 -

NCHH-pyridazine), 4.14 (1H, d, J=13Hz, OCHHAr), 4.66 (1H, d, J=13Hz, OCHHAr), 7.23-7.35 (3H, m, Ar-H), 7.50-7.56 (2H, m, ArH), 7.66 (2H, s, pyridazine-H), 7.71 (2H, s, ArH), 7.94 (1H, s, ArH), 9.11 (1H, m, 4H) MS (Cl⁺) m/z 496 (M⁺+1), 30%)

5

EXAMPLE 41

2-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino]methyl-1,3,5-triazine

10

The compound of Description 3 (2g), chloroacetamide hydrochloride (1.17g) and diisopropylethylamine (3.17ml) were dissolved in acetonitrile (10ml) and the resulting mixture was stirred at 60°C, under nitrogen, for 12h. The resulting mixture was evaporated and the residue was dispersed between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2x50ml) and dichloromethane (2x50ml). The combined organic fractions were washed with brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography on silica using 5% methanol in dichloromethane and gradient elution to 10% methanol, 1% aqueous ammonia in dichloromethane. This afforded the intermediate amidine as a semi-solid material, which was not further purified.

15

20

25

30

The intermediate amidine (2g) and 1,3,5-triazine (0.35g) were dissolved in acetonitrile (7ml) and heated at reflux for 12h. The solution was cooled and evaporated and the residue was purified by chromatography on silica using 50% petrol in ethyl acetate as eluent. This afforded the product as a crystalline solid which was recrystallised from hexane: mp 117-119°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.41-1.60 (2H, m, NCH₂CH₂CH₂), 1.81-1.94 (1H, m, NCH₂CHH), 2.12-2.21 (1H, m, NCH₂CHH), 2.34-

- 87 -

2.41 (1H, m, NCHH), 2.99-3.06 (1H, m, CHH), 3.26-3.30 (1H, J=15.0Hz, NCHH-triazine), 3.61 (1H, bs, CHO), 3.71 (1H, bs, CHPh), 3.80 (1H, d, J=15.0Hz, NCHH-triazine), 4.08 (1H, d, J=13.0Hz, OCHHAr), 4.63 (1H, d, J=13.0Hz, OCHHAr), 7.18-7.29 (3H, m, ArH), 7.48-7.52 (2H, m, ArH), 7.68 (2H, s, ArH), 7.13 (1H, s, ArH), 9.20 (2H, s, triazine-H). MS (CI⁺) m/z, 497 (M⁺+1, 100%).

EXAMPLE 42

10

5-[1(2S,3S)-3-((3-*t*-Butyl-5-methylphenyl)methyloxy)-2-(phenylpiperidino)methyl]-2,3-dihydro-3-oxo-1,2,4-triazole

The compound of Description 10 was reacted according to the procedure described in Example 35 to afford the title compound as a crystalline solid: mp 185-187°C. ¹H NMR (360MHz, CDCl₃) δ 1.22 (10H, m, C(CH₃)₃ + NCH₂CH₂CHH), 1.38-1.58 (2H, m, NCH₂CHHCHH), 1.98-2.26 (5H, m, CH₃ + NCHHCHH), 2.89 (1H, d, J=15.0Hz, NCHH-triazole), 2.96-3.04 (1H, m, NCHH), 3.29 (1H, bs, CHO), 3.56 (1H, bs, CHPh), 3.65 (1H, J=15.0Hz, NCHH-triazole), 4.13 (1H, d, J=12.0Hz, OCHHAr), 4.28 (1H, d, J=12.0Hz, OCHHAr), 6.53 (1H, s, ArH), 6.89 (1H, s, ArH), 7.00 (1H, s, ArH), 7.26-7.38 (3H, m, ArH), 7.45-7.50 (2H, m, ArH). MS (CI⁺) m/z 435 (M⁺+1, 60%). Found: C, 72.10; H, 7.94; N, 13.05. Calcd for C₂₆H₃₄N₄O₂: C, 71.86; H, 7.89; N, 12.89%.

EXAMPLE 43

30

2-[1(2S,3S)-3-((3,5-Dichlorophenyl)methyloxy)-2-(phenylpiperidino)methyl]imidazole dihydrochloride

- 88 -

The compound of Description 11 was reacted according to the procedure described in Examples 32/33, to afford the title compound: mp 129-131°C. ^1H NMR (360MHz, DMSO- d_6) δ 1.84-1.98 (2H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.14-2.24 (1H, m, NCH_2CHH), 2.44-2.62 (1H, m, NCH_2CHH), 3.09-3.20 (1H, m, NCHH), 3.69-3.86 (2H, m, $\text{NCHH} + \text{CHO}$), 4.25 (1H, d, $J=13.0\text{Hz}$, OCHHAr), 4.53 (1H, d, $J=13.0\text{Hz}$, OCHHAr), 4.83 (1H, d, $J=15.0\text{Hz}$, NCHH-imidazole), 4.91 (1H, bs, CHPh), 5.14 (1H, d, $J=15\text{Hz}$, NCHH-imidazole), 7.16-7.48 (10H, m, ArH), 7.84 (1H, bs, N-H). MS (CI^+) m/z 415 ($\text{M}+1^+$, 70%). Found: C, 50.71; H, 5.28; N, 8.05. $\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 2\text{H}_2\text{O}$ requires: C, 50.30; H, 5.56; N, 7.99%.

EXAMPLE 44

5-[(2S,3S)-3-((3-Chloro-5-methylphenyl)methyloxy)-2-phenylpiperidinomethyl]-2,3-dihydro-3-oxo-1,2,4-triazole

The compound of Description 12 was reacted according to the procedure described in Example 35 to afford the title compound as a white crystalline solid: mp 227-228°C. ^1H NMR (360MHz, DMSO- d_6) δ 1.35-1.55 (2H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.78-1.88 (1H, m, NCH_2CHH), 2.06-2.13 (2H, m, NCHHCHH), 2.20 (3H, s, CH_3), 2.73 (1H, d, $J=14.0\text{Hz}$, NCHH-triazole), 2.89 (1H, d, $J=11.0\text{Hz}$, NCHH), 3.32-3.39 (1H, m, CHO), 3.42 (1H, d, $J=14.0\text{Hz}$, NCHH-triazole), 3.47 (1H, s, CHPh), 3.86 (1H, d, $J=12.0\text{Hz}$, OCHH), 4.29 (1H, d, $J=12.0\text{Hz}$, OCHH), 6.65 (1H, s, ArH), 6.79 (1H, s, ArH), 7.07 (1H, s, ArH), 7.25-7.34 (3H, m, ArH), 7.51-7.53 (2H, m, ArH). MS (CI^+) m/z 412 (M^++1 , 20%). Found: C, 64.30; H, 6.13; N, 13.67. $\text{C}_{22}\text{H}_{25}\text{ClN}_4\text{O}_2$ requires: C, 63.99; H, 6.10; N, 13.57%.

- 89 -

EXAMPLE 45

5 5-[[[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy-2-(diphenylmethyl)pyrrolidinomethyl]-2,3-dihydro-3-oxo-1,2,4-
triazole

10 The compound of Description 13 was reacted with N-carbomethoxy-2-chloroacetamidrazone according to the procedure described in Example 35 to afford the product as a white crystalline solid. ¹H NMR (250MHz, CDCl₃) δ 1.92 (2H, m), 2.62 (1H, m), 2.90 (1H, d, J=15Hz), 3.14 (2H, m), 3.78 (2H, m), 4.08 (1H, m), 4.28 (2H, m), 7.1-7.4 (10H, m, ArH), 7.48 (2H, s, ArH), 7.77 (1H, s, ArH). MS (CI⁺) m/z 577 (M⁺+1, 100%).

15 EXAMPLE 46

20 5-[[[(2R,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy-2-(diphenylmethyl)pyrrolidinomethyl]-2,3-dihydro-3-oxo-1,2,4-
triazole

25 The compound of Description 14 was reacted with N-carbomethoxy-2-chloroacetamidrazone according to the procedure described in Example 35 to afford the title compound as a white crystalline solid. ¹H NMR (360MHz, CDCl₃) δ 2.00 (2H, m), 2.69 (1H, m), 3.03 (1H, t, J=7.5Hz), 3.26 (1H, d, J=14.5Hz), 3.32 (1H, d, J=14.5Hz), 3.68 (2H, s), 3.76 (1H, d, J=3.5Hz), 4.31 (1H, d, J=12.5Hz), 4.42 (1H, d, J=12.5Hz), 7.40-7.19 (10H, m, ArH), 7.64 (2H, s, ArH), 7.76 (1H, s, ArH). MS (CI⁺) m/z 577 (M⁺+1, 100%).

30

- 90 -

EXAMPLE 47

3-[(2S,3S)-3-((3,5-Dichlorophenyl)methoxy)-2-(diphenylmethyl)pyrrolidinomethyl]-1,2,4-triazole

5

The compound of Description 15 was reacted with N-formyl-2-chloroacetamidrazone according to the procedure in Example 16 to afford the title compound as a crystalline solid: mp 128-129°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.65 (1H, brs), 1.76 (1H, brs), 3.10 (2H, m), 3.61 (1H, d, J=12.0Hz), 3.92 (1H, brs), 4.01 (1H, brs), 4.22 (2H, m), 7.02 (2H, d, J=1.8Hz, ArH), 7.10 (1H, m, ArH), 7.14 (3H, m, ArH), 7.22 (2H, t, ArH), 7.39 (2H, d, ArH), 7.46 (3H, m, ArH). MS (CI⁺) m/z 493 (M⁺+1, 60%). Found: C, 65.95; H, 5.22; N, 11.33. Calcd for C₂₇H₂₆Cl₂N₄O: C, 65.72; H, 5.31; N, 11.35%.

15

EXAMPLE 48

5-[(2S,3S)-3-((3-*t*-Butyl-5-chlorophenyl)methoxy)-2-phenylpiperidinomethyl]-2,3-dihydro-3-oxo-1,2,4-triazole

20

The compound of Description 16 was reacted with N-carbomethoxy-2-chloroacetamidrazone, according to the procedure described in Example 35, to afford the title compound as a white crystalline solid: mp 181-182°C. MS (CI⁺) m/z 455 (M⁺+1, 100%). Found: C, 65.99; H, 6.87; N, 12.31. Calcd for C₂₅H₃₁ClN₄O: C, 66.47; H, 6.91; N, 12.45%.

25

30

EXAMPLE 49

5 5-[[[(2S,3S)-3-[(3-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinol)methyl]-2,3-dihydro-3-oxo-1,2,4-triazole
hydrochloride

The title compound was prepared according to the procedure described in Example 35, using the compound of Description 3 as starting material. The hydrochloride salt was
10 recrystallised from ethyl acetate-methanol to give a white crystalline solid: mp 265-266°C. ¹H NMR (360MHz, DMSO-d₆ + TFA) δ 1.75-1.95 (2H, m, CH₂), 2.04-2.30 (2H, m, CH₂), 3.20-3.32 (1H, m, NCHH), 3.58-3.69 (1H, m, NCHH), 3.90 (1H, d, J=15.0Hz, NCHH-triazole), 3.93 (1H, s, CHO), 3.94 (1H, d, J=15.0Hz, NCHH-triazole), 4.30 (1H, d, J=12.0Hz, OCHH), 4.73
15 (1H, bs, CHPh), 4.80 (1H, d, J=12.0Hz, OCHH), 7.42 (3H, brs, ArH), 7.56 (2H, brs, ArH), 7.89 (2H, s, ArH), 7.95 (1H, s, ArH). MS (CI⁺) m/z 501 (M⁺+1), 60%. Found: C, 51.41; H, 4.15; N, 10.58; Cl, 6.46. Calcd for C₂₃H₂₂F₆N₄O.HCl: C, 51.45; H, 4.32; N, 10.44; Cl, 6.60%.

EXAMPLE 50

25 3-[[[(2S,3S)-3-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-phenylpiperidinol)methyl]-1-methyl-1,2,4-triazole
hydrochloride

The compound of Example 30 (0.5g) was dissolved in methanol in a tube. Sodium (0.03g) and iodomethane (0.075ml)
30 were added and the container was sealed. The resulting solution was heated at 65°C for 1h, cooled and evaporated. The residue

- 92 -

was suspended between water and ethyl acetate. The organic layer was dried (MgSO₄), filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent. This afforded the product as a colourless oil, which was converted to the hydrochloride salt by addition of ethereal hydrogen chloride. The salt was recrystallised from ether/petrol. ¹H NMR (360MHz, DMSO-d₆) δ 1.70-1.84 (2H, m, CH₂), 2.12-2.51 (2H, m, CH₂), 3.36 (3H, s, NCH₃), 3.52 (1H, brs, CHHN), 3.73 (1H, brs, CHHN), 3.87 (1H, s, CHO), 4.25 (2H, m, CHH-triazole), 4.28 (1H, d, OCHHAr), 4.65 (1H, brs, NCHPh), 4.78 (1H, d, OCHHAr), 7.41 (3H, s, ArH), 7.60 (2H, brs, ArH), 7.93 (2H, s, ArH), 7.96 (1H, s, ArH), 8.05 (1H, s, CH=NH (triazole)); MS (CI⁺) m/z 499 (M⁺+1, 85%).

EXAMPLE 51

3-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl]-5-phenyl-1,2,4-oxadiazole hydrochloride

The compound of Description 3 was reacted with 3-chloromethyl-5-phenyl-1,2,4-oxadiazole according to the procedure described in Example 26. The product was characterised as its hydrochloride salt: mp 88-90°C. ¹H NMR (360MHz, CDCl₃, free base) δ 1.50-1.64 (2H, m, CH₂), 2.06-2.22 (2H, m, CH₂), 2.44-2.56 (1H, m, CHHN), 3.18-3.28 (1H, m, CHHN), 3.60 (1H, s, CHO), 3.66-3.74 (1H, d, J=15.0Hz, NCHH-oxadiazole), 3.78 (1H, s, CHPh), 3.88-3.98 (1H, d, J=15.0Hz, NCHH-oxadiazole), 4.02-4.10 (1H, d, J=12.0Hz, OCHHAr), 4.44-4.52 (1H, d, J=12.0Hz, OCHHAr), 7.28-7.64 (10H, m, ArH), 7.68 (1H, s, ArH), 8.08-8.18 (2H, m, ArH); MS (CI⁺) m/z 562 (M⁺+1).

- 93 -

EXAMPLE 52

5 3-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)
 methoxy)-2-phenylpiperidinolmethyl]-5-thiomethyl-1,2,4-
 triazole hydrochloride

 Sodium methoxide (.001g) was added to a solution of the
 compound of Example 17 (.10g) in ethanol (5ml) and the
 mixture was heated at reflux for 10 min. Methyl iodide
10 (0.012ml) in ethanol (1ml) was added and the mixture was
 heated at reflux for 3h. The solvent was then removed *in vacuo*
 and the residue was partitioned between ethyl acetate and
 water. The organic layer was dried (MgSO₄) and concentrated *in*
 vacuo. The residue was purified by chromatography on silica
15 using 50% ethyl acetate in petrol as eluent. The compound was
 isolated as the hydrochloride salt by treatment of the free base
 with methanolic hydrogen chloride: mp 105-107°C. ¹H NMR
 (360MHz, DMSO-d₆ + TFA) δ 1.73-1.91 (2H, m, CH₂), 2.05-2.20
 (1H, m, CHH), 2.21-2.30 (1H, m, CHH), 2.63 (3H, s, CH₃), 3.28
20 (1H, m, NCHHCH₂), 3.73 (1H, m, NCHHCH₂), 3.92 (1H, brs,
 CHO), 4.10 (2H, dd, J=20Hz, 14.5Hz, NCH₂), 4.29 (1H, d,
 J=13Hz, OCHH), 4.68 (1H, s, CHPh), 4.79 (1H, d, J=13Hz,
 OCHH), 7.42-7.48 (3H, m, ArH), 7.57 (2H, brs, ArH), 7.88 (2H, s,
 ArH), 7.95 (1H, s, ArH). MS (CI⁺) m/z 531 (M⁺+1, 44%). Found:
25 C, 51.29; H, 4.62; N, 9.79; Cl, 6.06. Calcd for C₂₉H₂₄F₆N₄OS.HCl:
 C, 50.84; H, 4.44; N, 9.88; Cl, 6.25%.

EXAMPLE 53

30 5-[(2S,3S)-3-((3,5-Dichlorophenyl)methoxy)-2-
 phenylpiperidinolmethyl]-2,3-dihydro-3-oxo-1,2,4-triazole

- 94 -

The compound of Description 11 was reacted according to the procedure described in Example 35 to afford the title compound which was recrystallised from hot dimethylformamide: mp >220°C. ¹H NMR (360MHz, DMSO-d₆, 353K) δ 1.45-1.58 (2H, m, CH₂), 1.81-1.95 (1H, m, CHH), 2.02-2.12 (1H, m, CHH), 2.18 (1H, dt, J=2.5, 11.5Hz, NCHHCH₂), 2.82 (1H, d, J=14.2Hz, NCHH), 2.94 (1H, brd, NCHHCH₂), 3.40 (1H, d, J=14.5Hz, NCHH), 3.45 (1H, d, CHO), 3.52 (1H, d, CHPh), 3.91 (1H, d, J=12.5Hz, OCHH), 4.34 (1H, d, J=12.5Hz, OCHH), 7.21-7.37 (5H, m, ArH), 7.47-7.55 (3H, m, ArH).

EXAMPLE 54

4-[(2R*,3R*)-3-((3-Carbomethoxyphenyl)methyloxy)-2-phenylpiperidinol)methyl]pyridinium dichloride

The compound of Description 17 was reacted with 4-picolyl chloride according to the procedure described in Example 4 to afford the title compound. ¹H NMR (250MHz, CDCl₃) δ 1.42-1.61 (2H, m, NCH₂CH₂CH₂), 1.98-2.18 (3H, m, NCHHCH₂), 2.87-3.04 (2H, m, NCHH-pyridine + NCHH), 3.31-3.39 (1H, m, CHO), 3.48-3.54 (1H, m, NCHPh), 3.86 (1H, d, J=14Hz, NCHH-pyridine), 3.93 (3H, s, OCH₃), 4.06 (1H, d, J=11Hz, OCHHAr), 4.30 (1H, d, J=11Hz, OCHHAr), 7.12 (1H, m, ArH), 7.22-7.39 (6H, m, ArH), 7.45-7.56 (2H, dd, pyridine-H), 7.77 (1H, bs, ArH), 7.85-7.92 (1H, ArH), 8.46-8.55 (2H, dd, pyridine-H). MS (CI⁺) m/z 417 (M⁺+1, 50%). Found: C, 64.10; H, 6.06; N, 5.62. C₂₆H₂₈N₂O₃·2HCl requires: C, 63.80; H, 6.18; N, 5.72%.

30

- 95 -

EXAMPLE 554-[[[(2R*,3R*)-3-((3-Carboxamidophenyl)methyloxy)-2-phenylpiperidino]methyl]pyridine

5

The compound of Description 18 was reacted with 4-picolyl chloride according to the procedure described in Example 4 to afford the title compound. ¹H NMR (360MHz, CDCl₃) 1.43-1.56 (2H, m, NCH₂CH₂CH₂), 2.00-2.17 (3H, m, NCHHCH₂), 2.88-3.04 (2H, m, NCHH + NCHHAr), 3.35 (1H, m, CHO), 3.54 (1H, bs, CHPh), 3.83 (1H, d, J=14.5Hz, NCHHAr), 4.08 (1H, d, J=12Hz, OCHHAr), 4.35 (1H, d, J=12Hz, OCHHAr), 5.6-6.16 (2H, bs, CONH₂), 7.11-7.74 (11H, m, ArH), 8.48 (2H, d, J=4Hz, pyridine-H). MS (CI⁺) m/z 402 (M⁺+1, 20%).

15

EXAMPLE 565-[[[(2R*,3R*)-3-((2-Methoxy-3-nitrophenyl)methyloxy)-2-phenylpiperidino]methyl]-3-methyl-1,2,4-oxadiazole

20

The compound of Description 19 was reacted according to the procedure described in Example 2 to afford the title compound. ¹H NMR (360MHz, CDCl₃) δ 1.48-1.64 (2H, m, NCH₂CH₂CH₂), 2.09-2.25 (2H, m, NCH₂CH₂), 2.37 (3H, s, CH₃), 2.41-2.51 (1H, m, NCHH), 3.12-3.20 (1H, m, NCHH), 3.59 (1H, bs, CHO), 3.64 (1H, bs, CHPh), 3.73 (1H, d, J=16Hz, NCHH-het), 3.80 (3H, s, OCH₃), 3.91 (1H, d, J=16Hz, NCHH-het), 3.98 (1H, d, J=13Hz, OCHHAr), 4.48 (1H, d, J=13Hz, OCHHAr), 6.78 (1H, d, J=9Hz, H), 7.22-7.37 (3H, m, ArH), 7.48-7.54 (2H, bd, ArH), 8.09-8.14 (1H, dd, J=9Hz, J=3Hz, ArH), 8.15-8.18 (1H, d, J=3Hz, ArH). MS (CI⁺) m/z 439 (M⁺+1, 100%).

30

- 96 -

EXAMPLE 57

3-Amino-5-[(2R*,3R*)-3-((5-amino-2-methoxyphenyl)methoxy)-2-phenylpiperidinol)methyl]-1,2,4-oxadiazole

5

The compound of Description 20 was reacted according to the procedure described in Example 1 to afford the title compound. ¹H NMR (360MHz, CDCl₃) δ 1.41-1.60 (2H, m, NCH₂CH₂CH₂), 2.13-2.24 (2H, m, NCH₂CH₂), 2.31 (1H, m, NCHH), 3.12-3.21 (1H, m, NCHH), 3.39 (1H, d, J=16Hz, NCHH-het), 3.47 (1H, m, CHO), 3.56 (1H, m, NCHPh), 3.61 (3H, s, OCH₃), 3.82 (1H, d, J=16Hz, NCHH-Het), 4.13 (1H, d, J=13Hz, OCHHAr), 4.34 (1H, d, J=13Hz, OCHHAr), 5.17 (2H, bs, NH₂), 6.38 (1H, bs, ArH), 6.43-6.48 (1H, m, ArH), 6.54-6.58 (1H, d, J=8.5Hz, ArH), 7.26-7.58 (3H, m, ArH), 7.48-7.54 (2H, m, ArH).

15

EXAMPLE 58

6-[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinol)methyl]uracil

20

The compound of Description 3 was reacted with 6-(chloromethyl)uracil following the conditions described in Example 4 to afford the title compound. ¹H NMR (360MHz, CDCl₃) 1.52-1.71 (2H, m, NCH₂CH₂CH₂), 1.99-2.25 (3H, m, NCHHCH₂), 2.69 (1H, d, J=16Hz, NCHH-uracil), 2.92-3.01 (1H, m, NCHH), 3.38-3.40 (1H, m, CHO), 3.52-3.62 (2H, m, NCHH-uracil + NCHPh), 4.08 (1H, d, J=12Hz, OCHHAr), 4.49 (1H, d, J=12Hz, OCHHAr), 5.41 (1H, s, H_A), 7.32-7.40 (5H, m, ArH), 7.50 (2H, s, H), 7.56 (1H, s, H), 8.64-9.04 (2H, bs, NH + NH). MS

25

30

- 97 -

(CI⁺) m/z 528 (M+1⁺, 100%). C₂₅H₂₃N₃O₃F₆ requires C, 56.93; H, 4.40; N, 7.97%. Found C, 57.16; H, 4.03; N, 7.88%.

EXAMPLE 59

5

3-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-5-carboxamido-1,2,4-triazole

10

The compound of Description 1 was reacted with 2-chloro-N-carboxamidoacetamidhydrazone according to the procedure described in Example 35 to afford the title compound as a white solid: mp 195°C. ν_{\max} (KBr) 1680cm⁻¹; Found: C, 55.14; H, 4.58; N, 12.82. Calcd for C₂₄H₂₃F₆N₅O₂: C, 54.65; H, 4.40; N, 13.27%.

15

EXAMPLE 60

20

3-[[[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-5-cyano-1,2,4-triazole

25

The compound of Example 59 (0.61g) was dissolved in chloroform (10ml) and the resulting solution was cooled to 0°C in an ice bath. Triethylamine (2ml) was added followed by phosphorus oxychloride (1.2ml), dropwise. The solution was stirred at room temperature for 1h. The solvent was removed *in vacuo* and the residue was dispersed between chloroform and sodium hydrogen carbonate. The organic layer was washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica using 30% petrol in ethyl acetate as eluent. The product was isolated

30

- 98 -

as the hydrochloride salt using ethereal hydrogen chloride: mp 81°C. MS (CI⁺) m/z 510 (M⁺+1, 60%).

EXAMPLE 61

5

3-[(1S)-1-[(2S,3S)-3-[(3,5-Dichlorophenyl)methoxy]-2-phenylpiperidinoethyl]-1,2,4-triazole

(a) (±) N-Formyl-2-chloropropionamidohydrazone

10

Sodium methoxide (.162g) was added to a solution of 2-chloropropionitrile (10.5g) in anhydrous methanol (150ml) at 0° C. The reaction mixture was stirred at room temperature for 1h, then neutralised with acetic acid (.18ml). N-Formylhydrazine (7.04g) was added and the mixture was stirred overnight. The

15

resulting pink solution was concentrated *in vacuo* to give the title compound as a pink solid.

(b) The compound of Description 11 (5.9g) was dissolved in dimethylformamide (46ml) and N-formyl-2-chloropropionamidohydrazone (3.5g) was added, followed by potassium carbonate (5.7g). The mixture was stirred at room temperature for 2h, then diluted with xylene (150ml) and heated at reflux for 2h. When cool, the mixture was filtered and concentrated *in vacuo* to afford a brown residue. Crude ¹H NMR indicated a mixture of diastereoisomers in 3:1 ratio. The residue

20

25

30

was purified by medium pressure chromatography (Lobar) on silica using 4% methanol in dichloromethane as eluent. The first product eluted, diastereoisomer 1, was isolated as a foam which was recrystallised from ether-hexane: mp 105-107°C ¹H NMR (360MHz, CDCl₃) δ 1.31 (3H, d, J=7.0Hz, -CHCH₃), 1.52-1.59 (2H, m, NCH₂CHHCHH), 2.02-2.05 (1H, m, NCH₂CHH), 2.05-2.16 (1H, m, NCH₂CH₂CHH), 2.51 (1H, t, J=11.5Hz, NCHH),

- 99 -

2.62 (1H, m, NCHH), 3.56 (1H, s, CHO), 3.77 (1H, s, CHPh),
3.99 (1H, d, J=12.0Hz, OCHH), 4.22 (1H, q, J=7.0Hz, -CHCH₃),
4.30 (1H, d, J=12.0Hz, OCHH), 6.89 (2H, d, J=2.0Hz, ArH), 7.21
(1H, t, J=2.0Hz, ArH), 7.3-7.4 (3H, m, ArH), 7.40-7.47 (2H, m,
5 ArH), 7.89 (1H, s, triazole-2H). MS (CI⁺) m/z.

EXAMPLE 62

10 3-[1(1R)-1-[(2S,3S)-3-[(3,5-Dichlorophenyl)methoxy]-2-phenylpiperidino]ethyl]-1,2,4-triazole

The second product isolated from the column described in
Example 61 was recrystallised from ether to afford the title
compound whose stereochemistry was established from ¹H NMR
15 n.O.e. experiments: mp 132-134°C ¹H NMR (360MHz, DMSO-d₆)
δ 1.06-1.15 (1H, m, NCH₂CH₂CHH), 1.35 (3H, d, J=7.0Hz,
CHCH₃), 1.34-1.42 (1H, m, NCH₂CHH), 1.66-1.85 (2H, m,
NCHHCHH), 1.98-2.02 (1H, m, NCH₂CH₂CHH), 3.01-3.03 (1H,
d, J=10.5Hz, NCHH), 3.39 (1H, s, CHO), 3.86 (1H, d, J=13.0Hz,
20 OCHH), 3.98 (1H, q, J=7Hz, CHCH₃), 4.33 (1H, d, J=13.0Hz,
OCHH), 6.92 (1H, d, J=2.0Hz, ArH), 7.26-7.46 (6H, m, ArH,

EXAMPLE 63

25 3-[1(2S,3S)-3-[(2,3-Dimethylphenyl)methoxy]-2-phenylpiperidinolmethyl]-1,2,4-triazole

Following the method described in Example 16, the
compound of Description 23 (100mg) was reacted with 69mg of
30 N-formyl-2-chloroacetamidohydrazone, to give the title
compound. ¹H NMR (CDCl₃) δ 1.50 (2H, m), 1.94 (3H, s), 2.0-

- 100 -

2.35 (3H, m), 2.2 (3H, s), 3.02 (1H, m), 3.45 (2H, m), 3.57 (1H, s),
3.95 (1H, br s), 3.95 (1H, d, J=11Hz), 4.26 (1H, d, J=11Hz), 6.86
(1H, d, J=7Hz), 7.06 (1H, d, J=7Hz), 7.2-7.5 (6H, m), 7.7 (1H, br
s).

5

The following compounds were prepared by the procedure
described in Example 35.

EXAMPLE 64

10

5-[[[(2S,3S)-3-((2,3-Dimethylphenyl)methoxy)-2-
phenylpiperidinol)methyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

15

The compound of Description 23 was used as starting
material. ¹H NMR (CDCl₃) δ 1.4-1.55 (2H, m), 1.89 (3H, s), 1.9-
2.2 (3H, m), 2.15 (3H, s), 2.91 (1H, d, J=15Hz), 2.95 (1H, m),
3.28 (1H, s), 3.50 (1H, s), 3.66 (1H, d, J=15Hz), 4.06 (1H, d,
J=12Hz), 4.29 (1H, d, J=12Hz), 6.77 (1H, d, J=7Hz), 6.9 (1H, t,
J=7Hz), 6.97 (1H, d, J=7Hz), 7.2-7.45 (5H, m).

20

EXAMPLE 65

25

5-[[[(2S,3S)-2-Phenyl-3-((3-(trifluoromethyl)phenyl)
methoxy)piperidinol)methyl]-3-oxo-1,2,4-triazole

30

The compound of Description 21 was used as starting
material. ¹H NMR (CDCl₃) δ 1.5 (2H, m), 1.9-2.2 (3H, m), 2.91
(1H, d, J=15Hz), 3.0 (1H, m), 3.3 (1H, s), 3.5 (1H, s), 3.64 (1H, d,
J=15Hz), 4.12 (1H, d, J=12Hz), 4.41 (1H, d, J=12Hz), 7.0-7.45
(9H, m), 9.9 (2H, br s).

- 101 -

EXAMPLE 66

5 5-[[[(2S,3S)-3-[(3,4-Dichlorophenyl)methoxy]-2-phenylpiperidinolmethyl]-3-oxo-1,2,4-triazole

 The compound of Description 22 was used as starting material. ¹H NMR (CDCl₃) δ 1.5 (2H, m), 1.85-2.2 (3H, m), 2.88 (1H, d, J=15Hz), 3.0 (1H, m), 3.27 (1H, s), 3.48 (1H, s), 3.67 (1H, d, J=15Hz), 4.05 (1H, d, J=12Hz), 4.35 (1H, d, J=12Hz), 6.7 (1H, br d, J=7Hz), 6.95 (1H, br s), 7.16 (1H, d, J=7Hz), 7.2-7.45 (5H, m), 9.8 (1H, br s), 10.5 (1H, br s).

EXAMPLE 67

15 5-[[[(2S,3S)-3-[(3-*t*-Butylphenyl)methoxy]-2-phenylpiperidinolmethyl]-3-oxo-1,2,4-triazole

20 The compound of Description 24 was used as starting material. ¹H NMR (CDCl₃) δ 1.23 (9H, s, C(CH₃)₃), 1.40-1.51 (2H, m, CH₂), 1.82-1.85 (1H, m, CHH), 2.01-2.14 (2H, m, CHH and NCHH), 2.74 (1H, d, J=14Hz, NCHH-triazolone), 2.88 (1H, m, NCHH), 3.38 (1H, d, J=14Hz, NCHH-triazolone), 3.40 (1H, m, NCHCHO), 3.51 (1H, s, NCHCHO), 3.85 (1H, d, J=12Hz, OCHH), 4.23 (1H, d, J=12Hz, OCHH), 6.80-6.82 (1H, m, ArH), 7.06-7.34 (6H, m, ArH), 7.53-7.55 (2H, m, ArH), 11.16 (1H, s, NH), 11.24 (1H, s, NH); MS (CI⁺) m/z 420 (M⁺+1, 10%). Found: C, 71.51; H, 7.51; N, 13.08. Calcd. for C₂₅H₃₂N₄O: C, 71.40; H, 7.67; N, 13.32%.

30

- 102 -

EXAMPLE 68

5 5-[[[(2R*,3R*)-3-((3,5-Dimethylphenyl)methoxy)-2-phenylpiperidinol)methyl]-3-oxo-1,2,4-triazole

 The compound of Description 25 was used as starting material. ¹H NMR (360MHz, DMSO-d₆) δ 1.41-1.47 (2H, m, CH₂), 1.81-1.85 (1H, m, CHH), 2.05-2.11 (2H, m, CHH and NCHH), 2.15 (6H, s, CH₃), 2.72 (1H, d, J=14Hz, NCHH-triazolone), 2.86-2.89 (1H, m, NCHH), 3.36 (1H, d, J=2.5Hz, CHO), 3.40 (1H, d, J=14Hz, NCHH-triazolone), 3.44 (1H, brs, CHPh), 3.82 (1H, d, J=12Hz, OCHH), 4.20 (1H, d, J=12Hz, OCHH), 6.50 (2H, s, ArH), 6.79 (1H, s, ArH), 7.25-7.33 (3H, m, ArH), 7.51-7.53 (2H, m, ArH), 11.16 (1H, s, NH), 11.25 (1H, s, NH).

EXAMPLE 69

20 (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(3-(1,2,4-triazolyl))piperidine

 1-Hydroxybenzotriazole hydrate (308mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (436mg), triethylamine (0.3ml) and 1,2,4-triazole-3-carboxylic acid (129mg) were dissolved in dimethylformamide (5ml) and the resulting mixture was stirred for 15 min. The compound of Description 3 (0.5g) was added and the resulting mixture was stirred at room temperature for 12h. The reaction mixture was diluted with water (100ml) and the product was extracted into ethyl acetate (3 x 50ml). The organic fractions were washed

- 103 -

successively with citric acid (aqueous), water, potassium carbonate and brine, then dried (MgSO_4) filtered and concentrated. The residue was purified by column chromatography on silica using 70% ethyl acetate in hexane as eluant. The product was recrystallised from ethyl acetate/petrol to afford a crystalline white solid: mp 77-79°C. MS (CI-) m/z 478 ((M-HF)⁻, 100%).

EXAMPLE 70

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy-1-(1-oxo-2-pyrid-4-yl)ethyl-2-phenylpiperidinium hydrochloride

The compound of Description 3 was reacted with 4-pyridylacetic acid following the procedure outlined in Example 69. This afforded a colourless oil which was treated with ethereal hydrogen chloride and the solid obtained was recrystallised from benzene/hexane. MS (CI+) m/z 523 (M⁺+1, 100%). Found: C, 54.67; H, 4.86; N, 4.66; Cl, 6.16. Calcd. for $\text{C}_{27}\text{H}_{24}\text{F}_6\text{N}_2\text{O}_2 \cdot 2\text{H}_2\text{O}$: C, 54.50; H, 4.91; N, 4.70; Cl, 5.96%.

EXAMPLE 71

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy-1-(2-oxo-2-pyrid-3-yl)ethyl-2-phenylpiperidine

3-(Bromoacetyl)pyridinium hydrobromide (336mg) was dissolved in dimethylformamide (3ml) and to this solution was added the compound of Description 3 (440mg) followed by potassium carbonate (550mg). The mixture was stirred at room temperature for 2h, diluted with water and extracted into ethyl

- 104 -

acetate. The organic phase was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography on silica using 70% ether in hexane as eluant and further purified by medium pressure chromatography (Lobar) using ethyl acetate in hexane (60:40) as eluant. ¹H NMR (250MHz, DMSO-d₆) δ 1.4-1.6 (2H, m), 1.8-1.98 (1H, m, CHH), 2.06-2.2 (1H, m, CHH), 2.5-2.6 (1H, m), 2.9-3.0 (1H, m), 3.54 (1H, d, NCHHCO), 3.62 (1H, brs, CHO), 3.74 (1H, d, CHPh), 3.84 (1H, d, OCHH), 7.2-7.3 (2H, m, ArH), 7.38-7.5 (3H, m, ArH), 7.5 (1H, dd, pyr-H), 7.85 (2H, s, ArH), 7.92 (1H, s, ArH), 8.14 (1H, dt, pyr-H), 8.62 (1H, dd, pyr-H), 8.94 (1H, d, pyr-H).

EXAMPLE 72

3-[(1S)-1-[(2S,3S)-3-[(3,5-Bis(trifluoromethyl)phenyl) methoxy]-2-phenylpiperidino]ethyl]-1,2,4-triazole

This was prepared from the compound of Description 3 and N-formyl-2-chloropropionamidohydrazone following the procedure described in Example 61. The first compound to be eluted from the column (using 3% methanol in dichloromethane as eluant on silica) was isolated and characterised as the title compound: mp 66-68°C. MS (CI⁺) m/z 499 ((M+1)⁺, 100%).

EXAMPLE 73

3-[(1R)-1-[(2S,3S)-3-[(3,5-Bis(trifluoromethyl)phenyl) methoxy]-2-phenylpiperidino]ethyl]-1,2,4-triazole

The second product isolated from the column described in Example 72 was recrystallised from ethyl acetate/hexane to

- 105 -

afford the title compound: mp 108-111°C. MS (CI⁺) m/z 499 ((M+1)⁺, 100%).

EXAMPLE 74

5 5-[(1S)-1-[(2S,3S)-3-[(3,5-Bis(trifluoromethylphenyl)methoxy]-2-phenylpiperidino)ethyl]-2,3-dihydro-3-oxo-1,2,4-triazole

10 This compound was prepared according to the procedure described in Example 35 using the compound of Description 3 and N-carbomethoxy-2-chloropropionamidohydrazone (ClCH(CH₃)C(=NH)NHNHCOOCH₃) as starting materials. ¹H NMR (CDCl₃) δ 0.94 (3H, d, J=7Hz), 1.4-1.58 (2H, m), 1.8 (1H, mc), 2.06-2.2 (1H, m), 2.26-2.4 (1H, m), 3.3 (1H, mc), 3.52 (1H, s), 3.64-3.72 (2H, m), 4.06 (1H, d, J=12Hz), 4.64 (1H, d, J=12Hz), 7.2-7.38 (3H, m), 7.6-7.7 (2H, m), 7.74 (2H, s), 7.94 (1H, s). MS (CI⁺) m/z 515 ((M+1)⁺, 23%).

EXAMPLE 75

20 3-[(2S,3S)-3-[(3,5-Dichlorophenyl)methoxy]-2-phenylpiperidino)methyl]-1,2,4-triazole

25 This was prepared from the compound of Description 11 according to the procedure described in Example 16 to afford the title compound: mp 208-212°C. MS (CI⁺) m/z 417 ((M+1)⁺, 100%).

- 106 -

EXAMPLE 76

5-[(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-(3-chlorophenyl)piperidinolmethyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

5 This was prepared from the compound of Description 26 according to the procedure described in Example 35: mp 125-127°C. ¹H NMR (360MHz, DMSO) δ 1.46-1.52 (2H, m), 1.9-1.95 (1H, m), 2.0-2.2 (2H, m) 2.92 (1H, d, J=15Hz, NCHHtriazolone), 2.98 (1H, mc), 3.35 (1H, s, CHO), 3.44 (1H, d, J=15Hz, NCHHtriazolone), 3.50 (1H, brs, CHPh), 3.96 (1H, d, J=12Hz, OCHH), 4.43 (1H, d, J=12Hz, OCHH), 7.15-7.22 (2H, m, ArH), 7.37-7.41 (2H, m, ArH), 7.48 (2H, s, ArH), 7.65 (1H, s, ArH). MS (CI⁺) m/z 535, 537 (M⁺+1, 100, 30%).

10

15 EXAMPLE 77

5-[(2S,3S)-3-((3,4-Dimethylphenyl)methoxy)-2-phenylpiperidinolmethyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

20 This compound was prepared according to the procedure described in Example 35 using the compound of Description 29 as starting material. ¹H NMR (CDCl₃) δ 1.37-1.55 (2H, m), 1.9-2.2 (3H, m), 2.1 (3H, s), 2.15 (3H, s), 2.85 (1H, d, J=15Hz), 2.97 (1H, m), 3.26 (1H, s), 3.51 (1H, s), 3.65 (1H, d, J=15Hz), 4.06 (1H, d, J=11Hz), 4.26 (1H, d, J=11Hz), 6.65 (2H, m), 6.9 (1H, d, J=8Hz), 7.2-7.45 (5H, m), 9.5 (1H, brs).

25

EXAMPLE 78

5-[(2S,3S)-3-((3-*i*Propoxyphenyl)methoxy)-2-phenylpiperidinolmethyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

- 107 -

This compound was prepared according to the procedure described in Example 35 using the compound of Description 30 as starting material. ¹H NMR (CDCl₃) δ 1.25 (6H, d, J=6Hz), 1.35-1.55 (2H, m), 1.9-2.2 (3H, m), 2.89 (1H, d, J=15Hz), 2.99 (1H, d, J=10Hz), 3.27 (1H, s), 3.51 (1H, s), 3.66 (1H, d, J=15Hz), 4.1 (1H, d, J=12Hz), 4.38 (1H, m), 6.48 (1H, d, J=7Hz), 6.57 (1H, s), 6.66 (1H, d, J=7Hz), 7.2-7.5 (5H, m).

EXAMPLE 79

5-[[(2S,3S)-3-((3-Fluoro-5-methylphenyl)methoxy)-2-phenylpiperidinolmethyl-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

This was prepared by the reaction of the compound of Description 27 according to the procedure outlined in Example 35: mp 228-229°C. ¹H NMR (360MHz, DMSO) δ 1.4-1.55 (2H, m, CH₂), 1.8-1.9 (1H, m, CH₂), 2.02-2.18 (2H, m, CH₂ and NCHH), 2.21 (3H, s, CH₃), 2.73 (1H, d, NCHH-het, J=14Hz), 2.87-2.90 (1H, d, NCHH, J=11Hz), 3.32-3.40 (1H, m, NCHCHO), 3.41 (1H, d, NCHH-het, J=14Hz), 3.46 (1H, s, NCHCHO), 3.87 (1H, d, OCHH-Ar, J=12.5Hz), 4.28 (1H, d, OCHH-Ar, J=12.5Hz), 6.50-6.55 (2H, m, ArH), 6.80-6.83 (1H, m, ArH), 7.29-7.31 (3H, m, ArH), 7.51-7.53 (2H, m, ArH), 11.18 (1H, s, NH), 11.28 (1H, s, NH). MS (CI⁺) m/z 397 (M⁺+1, 10%).

EXAMPLE 80

5-[[3-(3R*)-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-methyl-2-(2R*)-phenylpiperidinolmethyl-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

This was prepared from the compound of Description 28 according to the procedure outlined in Example 35. ¹H NMR

- 108 -

(360MHz, MeOD) δ 1.43 (3H, s, CH₃), 1.46 (1H, m), 1.91 (3H, m), 2.57 (2H, m), 2.98 (1H, d, J=15Hz, NCHH triazolone), 3.21 (2H, m), 3.58 (1H, d, J=15Hz, NCHH triazolone), 3.72 (1H, d, J=12Hz, OCHH), 4.36 (1H, d, J=12Hz, OCHH), 7.18 (1H, t, ArH), 7.25 (2H, t, ArH), 7.37 (2H, s, ArH), 7.53 (1H, s, ArH), 7.56 (1H, s, ArH), 7.71 (1H, s, ArH).

EXAMPLE 81

10 5-[[[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-(3-fluorophenyl)piperidinolmethyl]2,3-dihydro-(4H)-3-oxo-1,2,4-triazole

¹H NMR (CDCl₃) δ 1.42-1.62 (2H, m), 1.84-2.2 (3H, m), 2.86-3.1 (2H, m), 3.38-3.58 (3H, m), 4.08 (1H, d, J=12Hz, OCHH), 4.54 (1H, d, J=12Hz, OCHH), 6.92-7.04 (1H, m, ArH), 7.16-7.32 (3H, m, ArH), 7.54 (2H, s, ArH), 7.76 (1H, s, ArH).

EXAMPLE 82

20 3-[[[(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidinolmethyl]-1,2,4-triazine

(a) The compound of Description 3 (1g) was dissolved in dimethylformamide (8ml) and N-t-butyloxycarbonyl-2-chloroacetamidrazone (0.6g) was added, followed by potassium carbonate (0.9g). The mixture was stirred at room temperature overnight. The mixture was diluted with water, extracted with ethyl acetate and the organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica using ethyl acetate as eluant. This afforded the compound as a white solid which was

- 109 -

recrystallised from ether-hexane. ^1H NMR (360MHz, CDCl_3) δ 1.40 (9H, s, $(\text{CH}_3)_3$), 1.42-1.6 (3H, m), 2.13-2.2 (2H, m), 2.62 (1H, d, $J=15\text{Hz}$, $\text{NCHHC}=\text{NH}$), 3.07-3.10 (1H, m, CHHN), 3.36 (1H, d, $J=15\text{Hz}$, $\text{NCHHC}=\text{NH}$), 3.38 (1H, s, CHO), 3.57 (1H, brs, CHPh), 4.02 (1H, d, $J=12\text{Hz}$, OCHH), 4.45 (1H, d, $J=12\text{Hz}$, OCHH), 7.25-7.40 (5H, m, ArH), 7.53 (2H, s, ArH), 7.73 (1H, s, ArH).

(b) The Boc-protected amidrazone (1g) was dissolved in methanolic hydrogen chloride and stirred for 12h. The solvent was evaporated and the crude product was used in subsequent reactions without further purification.

(c) The amidrazone hydrochloride of (b) above (200mg) was dissolved in ethanol (2ml). Magnesium sulphate was added (100mg) and the mixture stirred for 30min. Triethylamine (0.06ml) was added followed by glyoxal (90mg, trimeric dihydrate). This mixture was allowed to stir for 12h. The solvent was removed *in vacuo* and the residue was dispersed between ethyl acetate and water. The organic layer was dried (MgSO_4) and concentrated to afford a brown oil. This was purified by column chromatography on silica using hexane in ethyl acetate (95%) to afford the title compound. ^1H NMR (360MHz, CDCl_3) δ 1.53-1.72 (2H, m, CH_2), 1.98-2.22 (2H, m, CH_2), 2.42-2.53 (1H, m, NCHH), 3.14-3.22 (1H, m, NCHH), 3.61 (1H, bs, CHO), 3.74-3.81 (2H, m, $\text{NCHPh} + \text{OCHH}$), 4.04 (1H, d, $J=12\text{Hz}$, NCHHtriazine), 4.19 (1H, d, $J=12\text{Hz}$, OCHH), 4.47 (1H, d, $J=12\text{Hz}$, NCHHtriazine), 7.24-7.37 (4H, m, ArH), 7.48-7.6 (4H, m, ArH), 7.70 (1H, s, ArH), 8.6 (1H, s, ArH). MS (CI^+) m/z 497 (M^++1 , 100%).

- 110 -

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 83A Tablets containing 1-25mg of compound

5		<u>Amount mg</u>		
	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
10	Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 83B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	26.0	50.0	100.0
15	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5
20	The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing			
25	1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.			

EXAMPLE 84 Parenteral injection

		<u>Amount mg</u>
30	Compound of formula (I)	1 to 100mg
	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg
	Water for Injections	to 1ml

- 111 -

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

5

EXAMPLE 85 Topical formulation

	<u>Amount mg</u>
Compound of formula (I)	1-10g
Emulsifying Wax	30g
10 Liquid paraffin	20g
White Soft Paraffin	to 100g

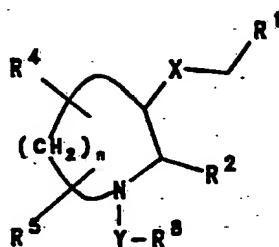
The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

15

- 112 -

CLAIMS:

1. A compound of formula (I), or a salt or
5 prodrug thereof:



(I)

15 wherein

n is 1, 2 or 3;

X represents O or S;

Y represents a hydrocarbon chain of 1, 2, 3 or
4 carbon atoms which may optionally be substituted by
20 oxo;

R¹ represents phenyl optionally substituted by
1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆ alkenyl,
C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl,
trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b,
25 -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b;

R² represents aryl selected from phenyl and
naphthyl; heteroaryl selected from indazolyl, thienyl,
furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl;
benzhydryl; or benzyl; wherein each aryl or heteroaryl
30 moiety may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo
or trifluoromethyl;

R⁴ and R⁵ may be present on any available
carbon atom of the azacyclic ring and each independently

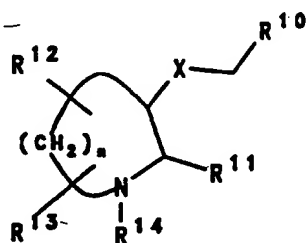
- 113 -

represent H, halo, C₁₋₆alkyl, oxo, CH₂OR^a, CO₂R^a or CONR^aR^b;

R⁸ represents an optionally substituted aromatic heterocycle; and

5 R^a and R^b each independently represent H, trifluoromethyl, C₁₋₆alkyl or phenyl optionally substituted by C₁₋₆alkyl, halo or trifluoromethyl.

10 2. A compound as claimed in claim 1 of formula (IA)



(IA)

20 wherein

n is 1, 2 or 3 and any carbon atom of (CH₂)_n may be substituted by R¹² and/or R¹³;

X represents O or S;

25 R¹⁰ represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^c, SR^c, SOR^c, SO₂R^c, -NR^cR^d, -NR^cCOR^d, -NR^cCO₂R^d, -CO₂R^c or -CONR^cR^d;

30 R¹¹ represents aryl selected from phenyl and naphthyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each aryl or heteroaryl moiety may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl;

- 114 -

R^{12} and R^{13} each independently represent H, halo, C_{1-6} alkyl, oxo, CO_2R^C or $CONR^C R^d$;

R^{14} represents C_{1-4} alkyl, optionally substituted by oxo, substituted by an optionally substituted aromatic heterocycle; and

R^C and R^d each independently represent H, C_{1-6} alkyl, phenyl optionally substituted by C_{1-6} alkyl, or halo or trifluoromethyl; or a salt or prodrug thereof.

10

3. A compound as claimed in claim 2 wherein n is 2 or 3; R^{12} and R^{13} each independently represent H, halo, C_{1-6} alkyl, CO_2R^C or $CONR^C R^d$; R^{14} represents C_{1-4} alkyl substituted by an optionally substituted 5- or 6-membered aromatic heterocycle; and R^C and R^d each independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl.

15

4. A compound as claimed in any preceding claim wherein R^1 represents phenyl substituted by one or more groups selected from C_{1-4} alkyl, trifluoromethyl and halo.

20

5. A compound as claimed in any preceding claim wherein R^2 represents benzhydryl or optionally substituted phenyl.

25

6. A compound as claimed in any preceding claim wherein R^8 represents optionally substituted thienyl, furyl, pyridyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, benzimidazolyl or benzoxazolyl.

30

- 115 -

7. A compound as claimed in any of claims 1 to 5 wherein R⁸ represents a substituted or unsubstituted 5- or 6-membered nitrogen-containing aromatic heterocycle.

5

8. A compound as claimed in claim 7 wherein R⁸ represents optionally substituted oxazolyl, oxadiazolyl, imidazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl or triazinyl, or
10 tetrazolyl substituted by C₁₋₆alkyl.

9. A compound as claimed in claim 8 wherein R⁸ represents unsubstituted triazolyl or triazolyl substituted by oxo or thioxo.

15

10. A compound as claimed in any preceding claim wherein n is 3.

11. A compound as claimed in claim 1 selected
20 from:

3-amino-5-[((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-oxadiazole;
5-[((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-3-methyl-1,2,4-
25 oxadiazole;
(+)-3-amino-5-[((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-oxadiazole;
3-[((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]pyridine;
30 2-[((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]pyridine;
2-[((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]benzimidazole;

- 116 -

- 5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]tetrazole;
2-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-4-methyl-1,3-thiazole;
5 (2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-1-(2-furoyl)-2-phenylpiperidine;
2-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]furan;
10 5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-3-bromo-1,2,4-oxadiazole;
5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-3-dimethylamino-1,2,4-oxadiazole;
15 (2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(2-thienoyl)piperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(2-thienyl)methylpiperidine;
20 5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-2,3-dihydro-4-methyl-3-thioxo-1,2,4-triazole;
3-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-triazole;
25 5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-2,3-dihydro-(4H)-3-thioxo-1,2,4-triazole;
5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-2-methyltetrazole;
30 5-[(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1-methyltetrazole;

- 117 -

- 3-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-5-dimethylamino-1,2,4-thiadiazole;
- 5 2-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-4,7-dimethylbenzoxazole;
- 2-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]benzoxazole;
- 10 4-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]oxazole;
- 2-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]pyrazine;
- 4-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-2-methyl-1,3-thiazole;
- 15 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-oxadiazole;
- 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-5-iodo-1,2,4-thiadiazole;
- 20 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-thiadiazole;
- 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-5-methoxy-1,2,4-thiadiazole;
- 25 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-triazole;
- 30 5-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-2,3-dihydro-(4H)-3-thioxo-1,2,4-triazole;

- 118 -

- 2-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-1-(p-toluenesulphonyl)imidazole;
- 5 2-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)imidazole;
- 4-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)imidazole;
- 10 5-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 5-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-3-(N,N-dimethylamino)-1,2,4-thiadiazole;
- 15 5-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)tetrazole;
- 5-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-2-methyltetrazole;
- 5-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-1-methyltetrazole;
- 20 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)pyridazine;
- 2-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-1,3,5-triazine;
- 5-(((2S,3S)-3-((3-t-butyl-5-methylphenyl)methoxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 25 2-(((2S,3S)-3-((3,5-dichlorophenyl)methoxy)-2-phenylpiperidino)methyl)imidazole;
- 5-(((2S,3S)-3-((3-chloro-5-methylphenyl)methoxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 30 5-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-diphenylmethyl)pyrrolidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;

- 119 -

- 5-[(2R,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-diphenylmethyl]pyrrolidino)methyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 3-[(2S,3S)-3-((3,5-dichlorophenyl)methoxy)-2-diphenylmethyl]pyrrolidino)methyl]-1,2,4-triazole;
- 5-[(2S,3S)-3-((3-t-butyl-5-chlorophenyl)methoxy)-2-phenylpiperidino)methyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 5-[(2S,3S)-3-((3,5-bistrifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 3-[(2S,3S)-3-((3,5-bistrifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-1-methyl-1,2,4-triazole;
- 3-[(2S,3S)-3-((3,5-bistrifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-5-phenyl-1,2,4-oxadiazole;
- 3-[(2R*,3R*)-3-((3,5-bistrifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]-5-thiomethyl-1,2,4-triazole;
- 5-[(2S,3S)-3-((3,5-dichlorophenyl)methoxy)-2-phenylpiperidino)methyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 4-[(2R*,3R*)-3-((3-carbomethoxyphenyl)methoxy)-2-phenylpiperidino)methyl]pyridine;
- 4-[(2R*,3R*)-3-((3-carboxamidophenyl)methoxy)-2-phenylpiperidino)methyl]pyridine;
- 5-[(2R*,3R*)-3-((2-methoxy-3-nitrophenyl)methoxy)-2-phenylpiperidino)methyl]-3-methyl-1,2,4-oxadiazole;
- 3-amino-5-[(2R*,3R*)-3-((5-amino-2-methoxyphenyl)methoxy)-2-phenylpiperidino)methyl]-1,2,4-oxadiazole;
- 6-[(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl]uracil;

- 120 -

- 3-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidino)methyl]-5-carboxamido-1,2,4-triazole;
- 5 3-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidino)methyl]-5-cyano-1,2,4-triazole;
- 3-((1S)-1-((2S,3S)-3-((3,5-dichlorophenyl)methyloxy)-2-phenylpiperidino)ethyl)-1,2,4-triazole;
- 10 3-((1R)-1-((2S,3S)-3-((3,5-dichlorophenyl)methyloxy)-2-phenylpiperidino)ethyl)-1,2,4-triazole;
- 3-(((2S,3S)-3-((2,3-dimethylphenyl)methyloxy)-2-phenylpiperidino)methyl)-1,2,4-triazole;
- 5-(((2S,3S)-3-((2,3-dimethylphenyl)methyloxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 15 5-(((2S,3S)-2-phenyl-3-((3-trifluoromethyl)phenyl)methyloxy)piperidino)methyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 5-(((2S,3S)-3-((3,4-dichlorophenyl)methyloxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 20 5-(((2S,3S)-3-((3-t-butylphenyl)methyloxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- 25 5-(((2R*,3R*)-3-((3,5-dimethylphenyl)methyloxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
- (2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(3-(1,2,4-triazolyl))piperidine;
- 30 (2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(1-oxo-2-pyrid-4-yl)ethyl-2-phenylpiperidine;
- (2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(2-oxo-2-pyrid-3-yl)ethyl-2-phenylpiperidine;

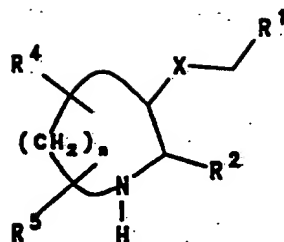
- 121 -

- 3-(1S)-1-((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)ethyl]-1,2,4-triazole;
 3-(1R)-1-((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)ethyl]-1,2,4-triazole;
 5 5-(1S)-1-((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)ethyl]-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 3-(((2S,3S)-3-((3,5-dichlorophenyl)methoxy)-2-phenylpiperidino)methyl)-1,2,4-triazole;
 10 5-(((2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-(3-chlorophenyl)piperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 5-(((2S,3S)-3-((3,4-dimethylphenyl)methoxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 15 5-(((2S,3S)-3-((3-i-propoxyphenyl)methoxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 5-(((2S,3S)-3-((3-fluoro-5-methylphenyl)methoxy)-2-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 20 5-((3-(3R*)-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-methyl-2-(2R*)-phenylpiperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 25 5-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-(3-fluorophenyl)piperidino)methyl)-2,3-dihydro-(4H)-3-oxo-1,2,4-triazole;
 3-(((2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidino)methyl)-1,2,4-triazine;
 30 and salts and prodrugs thereof.

12. A process for the preparation of a compound as claimed in claim 1, which process comprises:

(A) reacting a compound of formula (II):

- 122 -

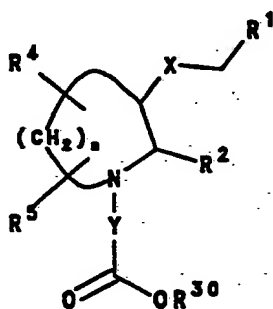


(II)

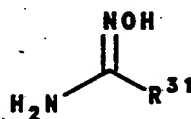
10 wherein R^1 , R^2 , R^4 , R^5 , X and n are as defined for formula (I), with a reagent suitable to introduce the group $Y-R^8$; or

(B) reacting a compound of formula (III) with a compound of formula (IV):

15



(III)



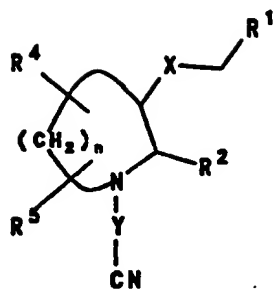
(IV)

25 wherein R^1 , R^2 , R^4 , R^5 , X, Y and n are as defined for formula (I), R^{30} represents an alkyl group and R^{31} represents H or a suitable substituent, in the presence of a base; or

(C) reacting a compound of formula (V):

30

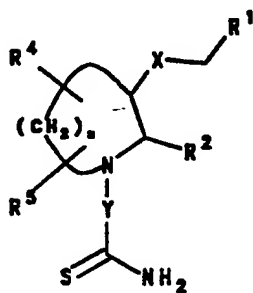
- 123 -



(V)

wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I), with an alkali metal azide; or

(D) reacting a compound of formula (VI):

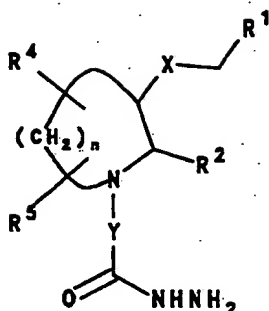


(VI)

wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I), with a compound of formula $Hal-CH_2C(=O)R^{60}$,
 25 where Hal represents halo and R^{60} represents H or a suitable substituent; or

(E) reacting a compound of formula (VII):

- 124 -

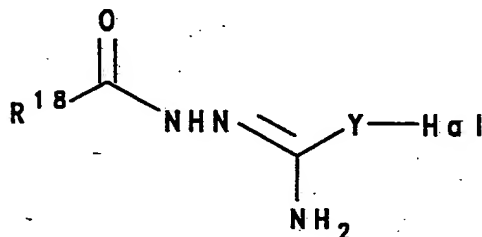


(VII)

wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I), with a compound of formula $R^{61}NCS$, wherein R^{61} is H or a suitable substituent, in the presence of a base; or

15

(F) reacting a compound of formula (II) as previously defined with a compound of formula (VIII):



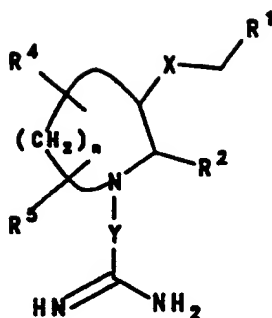
(VIII)

wherein Y and Hal are as previously defined and R^{18} is H or a group suitable as a substituent of the triazole ring, or convertible to such a group under the reaction conditions, in the presence of a base; or

30

(G) reacting a compound of formula (IX):

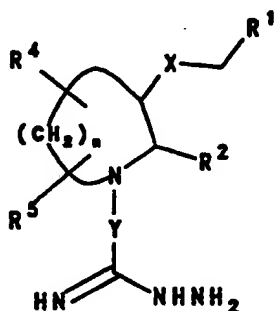
- 125 -



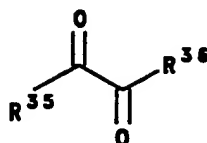
(IX)

wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I), with a substituted or unsubstituted triazine; or

- 15 (H) reacting a compound of formula (X) with a compound of formula (XI):



(X)



(XI)

wherein R^1 , R^2 , R^4 , R^5 , X , Y and n are as defined for formula (I) and R^{35} and R^{36} each independently represent H or a suitable substituent.

- 30 13. A process as claimed in claim 12 wherein, for (A) or (F), the base is an alkali metal carbonate.

14. A process as claimed in claim 12 or claim 13 wherein, for (A), the reagent suitable to introduce

- 126 -

the group $Y-R^8$ is R^8-Y-L where L is chloro, bromo, iodo, methylsulphonate or p-toluenesulphonate.

15 15. A process as claimed in claim 12 wherein,
for (B), the base is an alkali metal or an alkali metal
hydride.

10 16. A process as claimed in claim 12 wherein,
for (C), the alkali metal azide is sodium azide and the
reaction is effected in N-methylpyrrolidinone as solvent.

17. A process as claimed in claim 12 wherein,
for (D), R^{60} is H or C_{1-6} alkyl.

15 18. A process as claimed in claim 12 wherein,
for (E), the base is 1,8-diazabicyclo[5.4.0]undec-7-ene.

20 19. A process as claimed in claim 12 wherein,
for (F), R^{18} is methoxy.

20. A process as claimed in claim 12 wherein,
for (G), the reaction temperature is 80-90°C.

25 21. A process as claimed in claim 12 wherein,
for (H), R^{35} and R^{36} each represent H.

22. A compound as claimed in any one of claims
1 to 11 for use in therapy.

30 23. A pharmaceutical composition comprising a
compound as claimed in any one of claims 1 to 11 in
association with a pharmaceutically acceptable carrier.

- 127 -

24. A pharmaceutical composition as claimed in claim 23 further comprising a bronchodilator.

5 25. A method for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin-reducing amount of a compound according to claim 1.

10 26. A method according to claim 25 for the treatment or prevention of pain or inflammation.

15 27. A method according to claim 25 for the treatment or prevention of migraine.

28. A method according to claim 25 for the treatment or prevention of arthritis.

20 29. A method according to claim 25 for the treatment or prevention of postherpetic neuralgia.

25 30. A method for the treatment of a respiratory disease, which method comprises administration to a patient in need thereof of an effective amount of a compound as claimed in claim 1 and an effective amount of a bronchodilator.

30 31. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

- 128 -

32. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment of pain or inflammation.

5 33. A compound as claimed in any of claims 1 to 11 when prepared by the process of claim 12.

10 34. A process for preparing a composition as claimed in claim 23 which process comprises bringing a compound as claimed in any of claims 1 to 11 into association with a pharmaceutically acceptable carrier.

15 35. A compound, composition or process as claimed in any one of the preceding claims, substantially as herein before described.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/00788

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D413/06; C07D409/06;	C07D401/06; C07D403/06;	C07D417/06; A61K31/41; C07D405/06 A61K31/445
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K ; C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP,A,0 436 334 (PFIZER INC.) 10 July 1991 cited in the application *see definitions of R3, R2, R6 and R8, and examples, especially example 84*	1-24, 31-34
P,Y	EP,A,0 528 495 (MERCK SHARP & DOHME LTD.) 24 February 1993 cited in the application *see definitions of X,R1,R2*	1-24, 31-34
A	WO,A,9 005 729 (PFIZER INC) 31 May 1990	1-24, 31-34
P,Y	J. MED. CHEM. vol. 35, no. 26, 1992, pages 4911 - 4913 'Discovery of a Potent Substance P Antagonist: Recognition of the Key Molecular Determinant'	1-24, 31-34
	-/-	
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 29 JUNE 1993		Date of Mailing of this International Search Report 14. 07. 93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer SCRUTON-EVANS I.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,Y	EP,A,0 499 313 (MERCK SHARP & DOHME LTD.) 19 August 1992 *see definition of X* -----	1-24, 31-34

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9300788
SA 73117

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0436334	10-07-91	WO-A- 9109844	11-07-91
EP-A-0528495	24-02-93	WO-A- 9304040	04-03-93
WO-A-9005729	31-05-90	WO-A- 9005525	31-05-90
		CA-A- 2003441	23-05-90
		EP-A- 0409931	30-01-91
		US-A- 5162339	10-11-92
EP-A-0499313	19-08-92	JP-A- 5078354	30-03-93
		CA-A- 2060949	12-08-92